From Maxwell to Mitochondria, a Kirchhoff Computation

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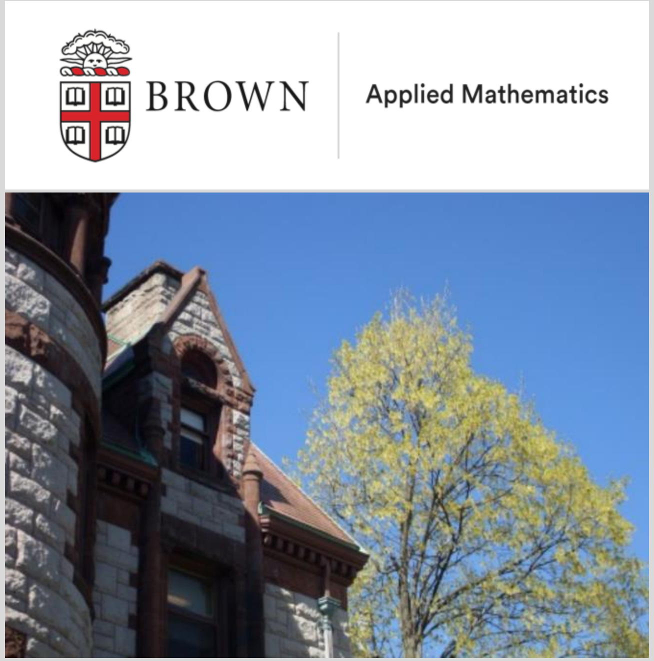
Current flow in circuits is the physical basis of computation in computers and the nervous system. We show how the Maxwell equations in circuits imply Kirchhoff's current law, but ***only*** when current includes the universal displacement current $\varepsilon_0 \partial \mathbf{E}/\partial t$.

Mitochondria house the respiratory chain of proteins that make ATP, that stores the chemical energy of life. Kirchhoff's current law makes possible computations of the $> 10^{18}$ atoms of the mitochondrion, as it made possible the computation of the Atlantic cable (Kelvin Heaviside), the nerve axon (Hodgkin Huxley), the lens of the eye (Mathias, Huaxiong Huang et a;), and the glia of the optic nerve bundle (Huaxiong Huang, Shixin Xu et al).

Thanks to Chi-Wang for inviting me

to



May 5, 2023

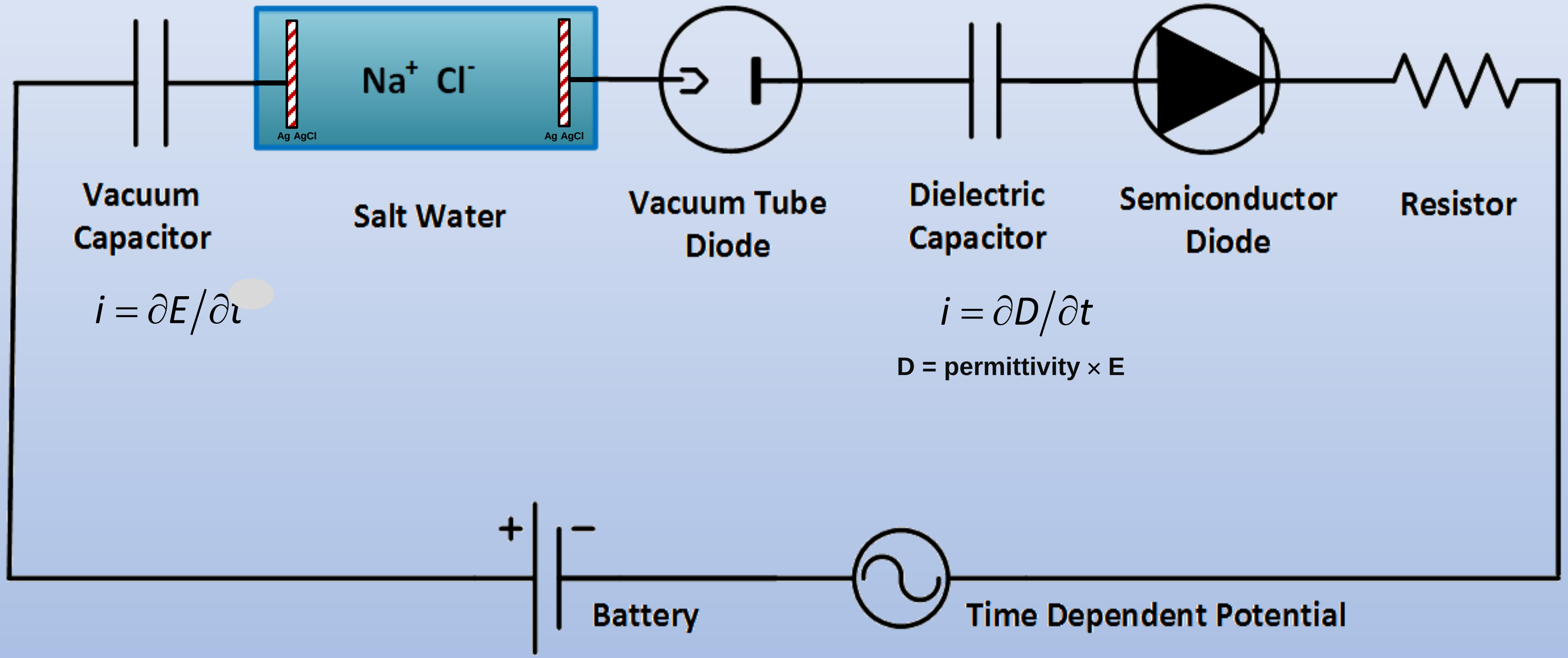
Kirchhoff’s Law is about Current

Physical Statement

The current that flows into a node flows out.
The current that flows in a wire is equal everywhere.
The current that flows in a series of components is equal everywhere.

NOTE Kirchhoff’s law is true at all times and in all conditions
as we shall prove

Kirchhoff Coupling: Total Current is the Same in Series Systems Independent of Mechanism of Charge Movement



$i = \partial E / \partial t$

$i = \partial D / \partial t$

D = permittivity × E

TRIVIAL and PROFOUND

Eisenberg (2016) Mass Action and Conservation of Current.
Hungarian Journal of Industry and Chemistry 2016 44:1-28
also arXiv:1502.07251 44:1-28.

Kirchhoff’s Law is about Current

Engineering Statement
Stochastic Signal Processing

Currents in a Classical Circuit are perfectly correlated with Coherence Function of 1.0

Another Talk
Another Time
Nicholson, Minh , Eisenberg
Coherence in an α-helix.
ACS Omega 2023 8:13920

$$X(f) \longrightarrow \boxed{H(f)} \longrightarrow Y(f)$$

$$C_{xy}(f) = \frac{|H(f)G_{xx}|^2}{G_{xx}(f)|H(f)|^2G_{xx}} = 1 \; when\, H(f) = \frac{Y(f)}{X(f)}$$

NOTE Kirchhoff’s law is true at all times and in all conditions
as we shall prove

Kirchhoff’s Law is about Current

Chemists find this
problematic

Currents in a series system are COUPLED
by Kirchhoff’s law,
<u>TRIVIAL and PROFOUND</u>
<u>No matter what the local mechanism of charge movement</u>
No matter what ions are carrying the current

NOTE Kirchhoff’s law is true at all times and in all conditions
as we shall prove

Kirchhoff’s Law is about Current

Biological Statement

A graph of one current *vs* another is a straight line

Currents in a series system are COUPLED

by Kirchhoff’s law,

TRIVIAL and PROFOUND

No matter what the local mechanism of charge movement

NOTE Kirchhoff’s law is true at all times and in all conditions

as we shall prove

What is Current?

This is a math department
So first

DEFINE CURRENT WITH EQUATIONS

Derivation

Physical Fact: $$\frac{1}{\mu_0}\,\mathbf{curl\ B} = \mathbf{J} + \boldsymbol{\varepsilon}_0\ \partial\mathbf{E}/\partial \boldsymbol{t}$$ ***Maxwell-Ampere***

J is the flux of charge with mass, however brief, small, or transient

J includes the polarization charge of dielectrics

Math Identity: $$\mathbf{div\ curl}\ anything = \mathbf{0}$$

Result:

Kirchhoff Current Law

$$\boxed{\mathbf{div}\left(\mathbf{J} + \boldsymbol{\varepsilon}_0\,\frac{\partial\mathbf{E}}{\partial \boldsymbol{t}}\right) = \mathbf{div\ curl\ B} = \mathbf{0}}$$

What is Current?

Physical Fact: $\frac{1}{\mu_0}\,\mathbf{curl\ B} = \mathbf{J} + \boldsymbol{\varepsilon_0 \partial E/\partial t}$ *Maxwell-Ampere*

J is the flux of charge with mass, however brief, small, or transient.
J includes the polarization charge of dielectrics.

Natural Definition of Total Current: $\boxed{\mathbf{J}_{\boldsymbol{total}} = \mathbf{J} + \boldsymbol{\varepsilon_0\ \partial E/\partial t}}$

Result:

Kirchhoff Current Law

$$\mathbf{div}\,\boldsymbol{J_{total}} = \mathbf{0}$$

For non-mathematicians

Div is Divergence

Divergence is an exact measure of what flows out of a region

When div equals zero, nothing flows in or out $\mathbf{div} = \mathbf{0}.$

When div $\mathbf{J}_{total} = \mathbf{0},$

$\mathbf{J}_{total}$ is exactly CONSERVED

All that flows in, flows out

For non-mathematicians

Div curl “Anything” = 0

NOT fancy math

Easy to prove, in every Graduate Physics Course

Div curl B = 0

Is an experimental fact

Key Result

Conservation of TOTAL Current

$$\mathbf{J}_{total}$$

Natural Definition of Total Current: $\mathbf{J}_{total} = \mathbf{J} + \varepsilon_0\, \partial\mathbf{E}/\partial t$

Result:

Kirchhoff Current Law

$$\mathrm{div}\ \mathbf{J}_{total} = 0$$

The previous slides were mathematically sufficient
But mathematicians are people

So we move on
to motivate the equations
with the underlying physics

What is Current?

**Current is Defined in Physics
as that which makes a magnetic field**

Current is NOT the Flow of Charge

How do we know that?

Magnetic Fields Exist in Vacuum

Charge and Current density are ZERO in a vacuum

Magnetic Fields in Vacuum Create Electromagnetic Waves

LIGHT

$$\mu_0 \varepsilon_0 \frac{\partial^2 \mathbf{E}}{\partial t^2} - \nabla^2 \mathbf{E} = 0$$

$c = 1/\sqrt{\varepsilon_0 \mu_0}$ = velocity of light

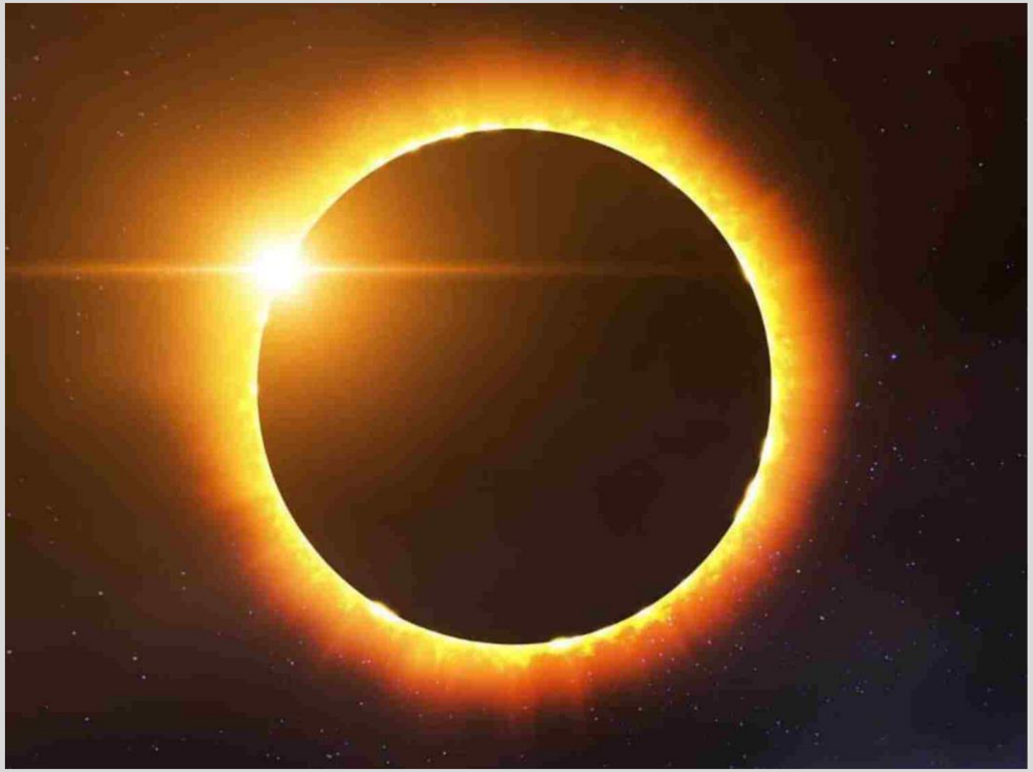
$$\mu_0 \varepsilon_0 \frac{\partial^2 \mathbf{B}}{\partial t^2} - \nabla^2 \mathbf{B} = 0$$

Light travels through the Vacuum of Space

ethereal current $\varepsilon_0 \partial \mathrm{E}/\partial t$ flows in vacuum of space,

once thought to be filled with an ‘aether’

Jeans 1908. The mathematical theory of electricity and magnetism.
Whittaker 1951. A History of the Theories of Aether & Electricity.
Simpson 1998. Maxwell on the Electromagnetic Field: A Guided Study.



$$\mu_0 \varepsilon_0 \frac{\partial^2 \mathbf{E}}{\partial t^2} - \nabla^2 \mathbf{E} = 0$$

Wave Equation
Corollary of
Maxwell Equations

$\boldsymbol{c = 1/\sqrt{\varepsilon_0 \mu_0}}$ **= velocity of light**

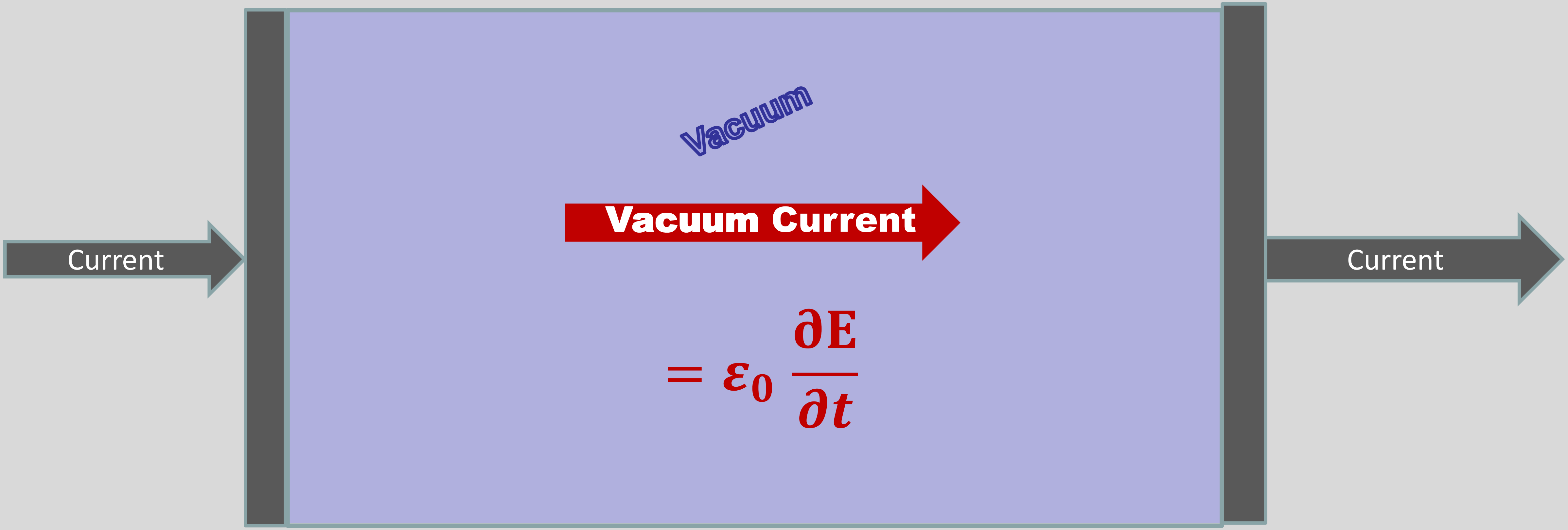
$$\mu_0 \varepsilon_0 \frac{\partial^2 \mathbf{B}}{\partial t^2} - \nabla^2 \mathbf{B} = 0$$

Well known Example

taught,

or should be taught,

In First Year of Physics



$$= \varepsilon_0 \frac{\partial \mathrm{E}}{\partial t}$$

Vacuum current = Ethereal current = Displacement Current
All are names for the same thing $\varepsilon_0\, \partial\mathrm{E}/\partial t$

Maxwell Ampere Law in a Vacuum
No known error between stars, inside atoms

$$\frac{1}{\mu_0}\,\mathbf{curl}\ \overset{\substack{\textbf{Magnetism}\\ \downarrow}}{\mathbf{B}} = \underbrace{\varepsilon_0\ \frac{\partial \mathbf{E}}{\partial t}}_{\textbf{CURRENT}}$$

Vacuum contains no charge
and thus flow of charge $\mathbf{J} = \mathbf{0}$

Fundamental Result of Physics

$$\varepsilon_0 \frac{\partial \mathrm{E}}{\partial t} \text{ is everywhere}$$

Displacement Current $\varepsilon_0\ \partial \mathrm{E}/\partial t$ is a Property of Space according to Theory of Relativity

Maxwell Equations and Relativity are almost the same thing

"**The special theory of relativity … was simply a systematic development of the electrodynamics of Clerk Maxwell and Lorentz**".

p. 57 of Einstein, A. 1934. *Essays in science,*
originally published as Mein Weltbild 1933,
translated from the German by Alan Harris. Open Road Media.

Electrodynamics and Relativity

Charge has a Special Place in physics

Charge (coulombs) does not vary
as it moves at velocity v,
even near the velocity of light c
Charge (coulombs) is “Lorentz Invariant”

Distance, time, and relativistic mass
Change Dramatically
near the velocity of light as $\sqrt{1 - v^2/c^2}$

Electrodynamics and Relativity

Charge has a Special Place in Physics

Displacement Current $\boldsymbol{\varepsilon_0\, \partial \mathrm{E}/\partial t}$ makes charge Lorentz Invariant

$\boldsymbol{\varepsilon_0\, \partial \mathrm{E}/\partial t}$ has a Special Place in Physics

Maxwell Ampere Law Everywhere

No known error, inside atoms or between stars

$$\frac{1}{\mu_0}\,\overset{\substack{\textbf{Magnetism}\\ \downarrow}}{\mathbf{curl}}\,\mathbf{B} = \mathbf{J} + \overbrace{\varepsilon_0\,\frac{\partial \mathbf{E}}{\partial t}}^{\substack{\textbf{Universal}\\ \textbf{Displacement}\\ \textbf{Current}}} = \mathbf{J}_{total}$$

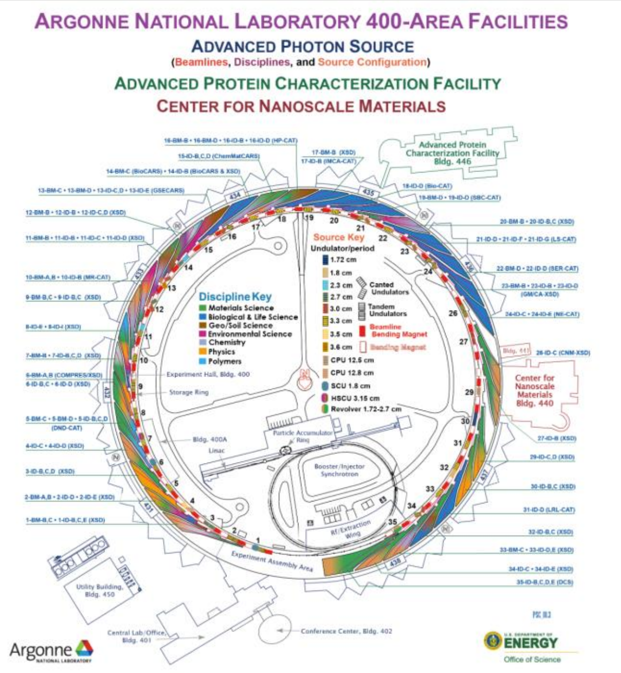
Fundamental <u>Experimental</u> Result
in Physics
$\varepsilon_0 \partial \mathrm{E}/\partial t$ exists everywhere, *e.g.,*
inside atoms

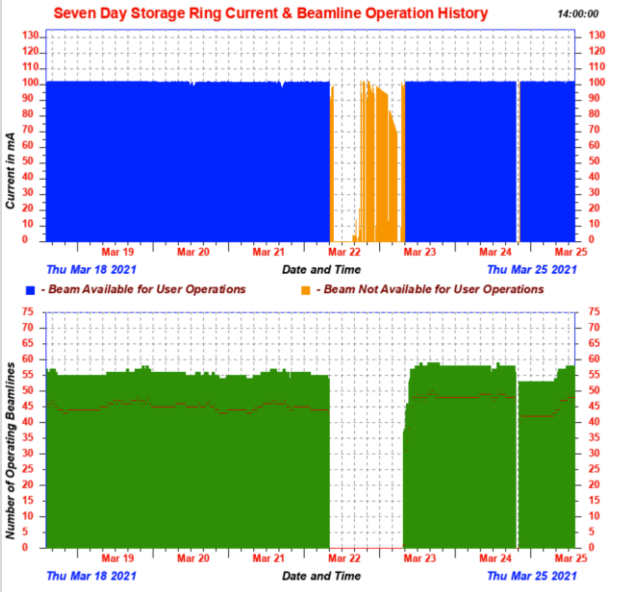
J is the flow of all charge,
however brief, small or transient.
J includes polarization charge of dielectrics

Advanced Photon Source Argonne National Laboratory

Error in Theory $< 10^{-10}$

Beam $\sim 10^{10}$ eV
Beam length 10^3 m
Tolerance $< 10^{-7}$ m
Beam Current 100 mA
Beam Power 10^9 watts





Source Internet

Maxwell-Ampere Equation Implies Conservation of Total Current

$$\frac{1}{\mu_0}\,\mathbf{curl\ B} = \mathbf{J}_{\boldsymbol{total}}$$

$\mathbf{J}_{\boldsymbol{total}}$ includes the flux of charge with mass, however brief, small, or transient.
$\mathbf{J}_{\boldsymbol{total}}$includes the polarization charge of dielectrics.

Identity

$$\mathbf{div\ curl}\ \mathit{anything} = \mathbf{0}$$

Kirchhoff Current Law for Fields

$$\mathbf{div\ J}_{\boldsymbol{total}} = \mathbf{div\ curl\ B} = \mathbf{0}$$

If $\mathbf{J}_{total}$ is conserved, J is not conserved

If $\mathbf{div}\,(\mathbf{J}+\boldsymbol{\varepsilon}_0\,\partial\mathbf{E}/\partial t)=\mathbf{0},\quad \mathbf{div}\,\mathbf{J}\neq\mathbf{0}$

The flux of charges is not conserved.

The current of charges accumulates
as ‘free’ charge ρ

by Continuity Equation $\mathbf{div}\,\mathbf{J}=-\varepsilon_0\,\partial\rho/\partial t \;\Rightarrow\; \mathbf{div}\,\mathbf{J}\neq\mathbf{0}$

Obvious,
But Widely Misunderstood

Paradigm Change

Usual derivation of Circuit Kirchhoff Discusses only flux J of charges

Derivation should discuss $\mathbf{J}_{total}$

Maxwell $\quad \text{div}\ \mathbf{J}_{total} = \mathbf{0}$

and

Classical Kirchhoff $\quad \text{div}\ \mathbf{J} = \mathbf{0}$

DISAGREE

Physical Note about Steady State $\partial \mathrm{E}/\partial t = 0$

Underlying physics is hidden by the special case $\varepsilon_0\, \partial \mathrm{E}/\partial t = 0$

The steady state ignores the charge that invariably* accompanies an E field,

usually at its boundaries

Physics prohibits general steady state

$\varepsilon_0\, \partial \mathrm{E}/\partial t \neq 0$ in general because fields

change in applications

*Gauss’ law, the first Maxwell Eqution

Mathematical Note about Steady State $\partial \mathrm{E}/\partial t = 0$

Studying electrodynamics always involves initial and boundary Conditions

<u>Careful</u> Treatment of Initial and Boundary Conditions shows that Charge $\boldsymbol{\rho(x, y, z; t)}$ ALWAYS accompanies an Electric field

Charge may be on boundaries or in the initial state, of course.

We have shown that Kirchhoff’s law for fields must include Displacement Current $\varepsilon_0\ \partial\mathrm{E}/\partial t$

Versions of Kirchhoff’s law
that do not include
Displacement Current $\varepsilon_0\ \partial\mathrm{E}/\partial t$
are incompatible with the Maxwell equations

MATHEMATICIANS NEED NOT WORRY

**When Kirchhoff’s law is corrected, classical application,
are well defined approximations
if a single dielectric constant is a good approximation (not bad in silicon, bad in ionic solutions, horrible in proteins).**

OTHER APPLICATIONS HAVE PROBLEMS

The fundamental understanding of atomic motion is changed when Kirchhoff's law is corrected

‘Everything’ is Coupled to ‘Everything Else’

as we shall see.

Atomic motion is then viewed as the motion of charges necessary to maintain conservation of total current
which is as universal and exact as the Maxwell equations themselves)

This revision changes the interpretation of how molecular machines work,
e.g., the transporters of protons and electrons that creat the 'storehouse of nearly all chemical energy in living systems' ATP

So far we have talked about
Conservation of Total Currentin general Fields
But not in circuits

What about Kirchhoff’s Current Law in Circuits?

We have shown that Kirchhoff’s law for fields must include Displacement Current $\varepsilon_0\ \partial\mathrm{E}/\partial t$

Versions of Kirchhoff’s Circuit law
that do not include
Displacement Current $\varepsilon_0\ \partial\mathrm{E}/\partial t$
are incompatible with the Maxwell equations

Kirchhoff’s Law of Circuits must include the Displacement Current

But including displacement current is not enough
To validate Kirchhoff’s Law in Circuits

All the total current must flow in branched networks
Circuit components must be ideal, including wires

All the total current must flow in branched networks

Circuit components must be ideal, including wires

Difficult to Specify in Theory

But

EASY TO CHECK IN EXPERIMENTS

EASY IN IDEALIZED CIRCUITS

Just include stray capacitances

But Difficult to Specify *a priori* in Realistic Models

Difficult to Specify in Realistic Models
But
EASY TO CHECK IN EXPERIMENTS

MEASURE THE CURRENTS

See if they add up

CHECK THE THEORY

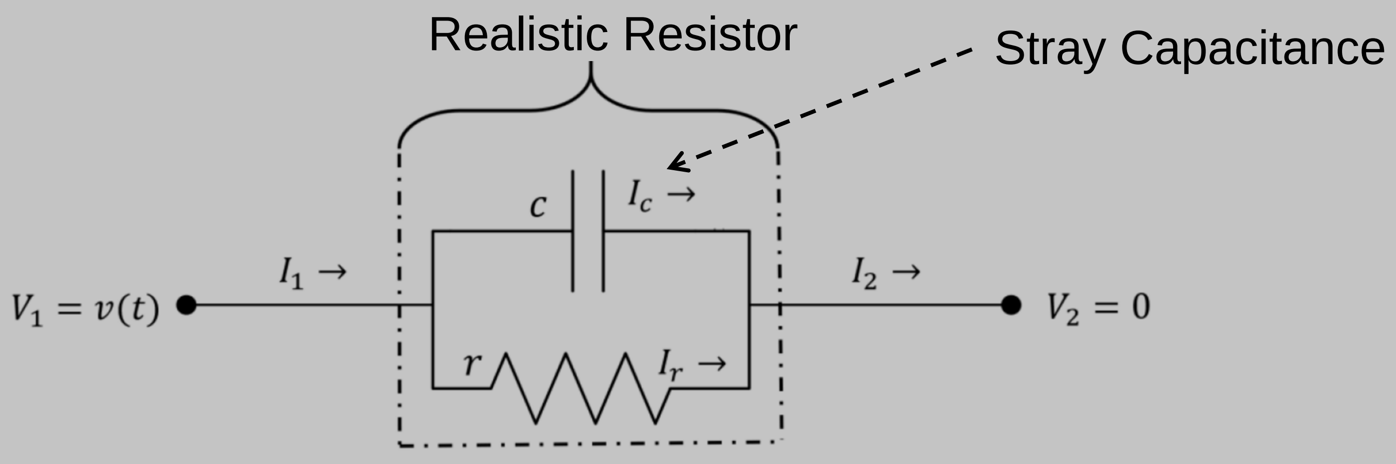
No textbooks include displacement current in Kirchhoff’s Circuit Law as far as my collaborators and I can determine

How can circuits work if they are designed with the wrong version of Kirchhoff’s Law?

How can circuits work if they are designed with the wrong version of Kirchhoff’s Law?

Answer:

Circuits are Expanded to include ‘Stray’ Capacitances And those include the universal displacement current


Realistic Resistor

Stray Capacitance

$$I_1 = I_2 = I_r + I_c$$

Numerical treatments of Electrodynamics must include the Displacement Current $\boldsymbol{\varepsilon_0\ \partial\mathrm{E}/\partial t}$

Numerical Treatments with dielectric constant $\boldsymbol{\varepsilon_r\varepsilon_0\ \partial\mathrm{E}/\partial t}$ include Displacement Current because $\boldsymbol{\varepsilon_r \geq 1}$

Optimal Numerical Treatment of Total Current is put forward in the following references

Ji, Lijie, Pei Liu, Zhenli Xu, and Shenggao Zhou. "Asymptotic Analysis on Dielectric Boundary Effects of Modified Poisson--Nernst--Planck Equations." *SIAM Journal on Applied Mathematics 78, no. 3 (2018): 1802-22.*

Qiao, Zhonghua, Zhenli Xu, Qian Yin, and Shenggao Zhou. "Structure-Preserving Numerical Method for Maxwell-Ampère Nernst-Planck Model." *Journal of Computational Physics 475 (2023/02/15/ 2023): 111845.*

Qiao, Z., Z. Xu, Q. Yin and S. Zhou (2023). "A Maxwell–Ampère Nernst–Planck Framework for Modeling Charge Dynamics." SIAM Journal on Applied Mathematics 83(2): 374-393.

Surprising PHYSICAL and Biophysical Consequences of Kirchhoff Field Law

OTHER APPLICATIONS HAVE PROBLEMS

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‘Everything’ is Coupled to ‘Everything Else’

as we shall see.

Atomic motion is then viewed as the motion of charges necessary to maintain conservation of total current
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This revision changes the interpretation of how molecular machines work,
e.g., the transporters of protons and electrons that creat the 'storehouse of nearly all chemical energy in living systems' ATP

Conservation of Current is Exact and Universal

So what?

(1) Current must always be described by Continuum Equations

Because of $\varepsilon_0\,\partial E/\partial t$

(2) Particle motion does NOT define Current

Contradicts Intuition

Current $\neq$ Flux of charge

Contradicts Intuition

Small Systems
REQUIRE
Continuum Description
of
Electric Current

Because of $\varepsilon_0\, \partial E/\partial t$

Current does NOT flow by hopping

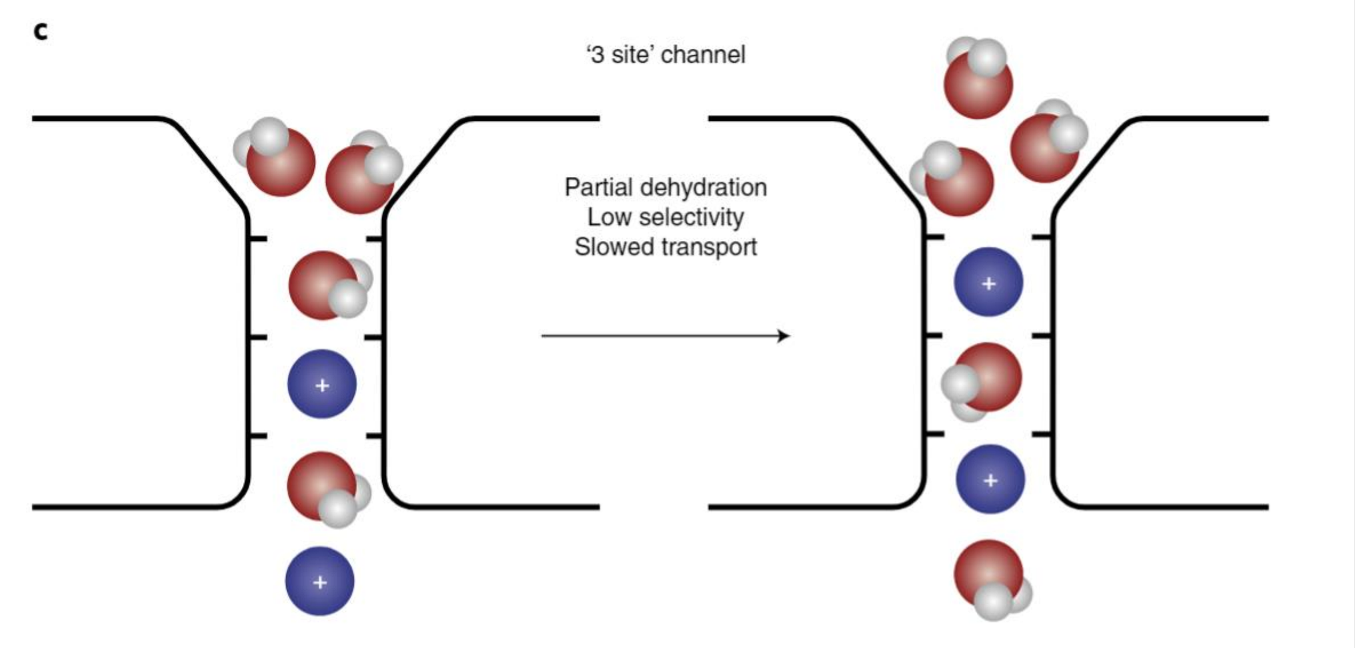
Current is independent of location in series systems

Particles can hop, total current cannot

What does this mean for Ion Channels?

Knock On and Knock Off of Ions
is
IRRELEVANT for the Total Current J_{total} Through the Channel

Paradigm Change



Corry (2018) 'The naked truth about K^+ selectivity'. Nature Chemistry 10:799-800.

Eisenberg (2020)
'Electrodynamics Correlates Knock-on and Knock-off: Current is Spatially Uniform in Ion Channels.'
Preprint on arXiv at 2002.09012

View of Channels has been focused on movements of individual ions in channels,

But

Total Current J_{total} is equal everywhere
in a one dimensional channel

Paradigm Change

Position does <u>not</u> appear in equations for total current J_{total} in a one dimensional channel

References and Proofs in
Eisenberg (2019) **Kirchhoff's Law can be Exact**. arXiv: 1905.13574

Eisenberg, Gold, Song, and Huang (2018)
What Current Flows Through a Resistor?
arXiv:1805.04814

Revolution in Biophysics

Total Current flow J_{total} is equal everywhere in a one dimensional system

Thermal Motion in Space does not appear in equations for flow of total current J_{total} in a one dimensional system

Thermal motion appears ONLY in time

Eisenberg (2020)
Electrodynamics Correlates Knock-on and Knock-off: Current is Spatially Uniform in Ion Channels.
Preprint on arXiv at https://arxiv.org/abs/2002.09012.

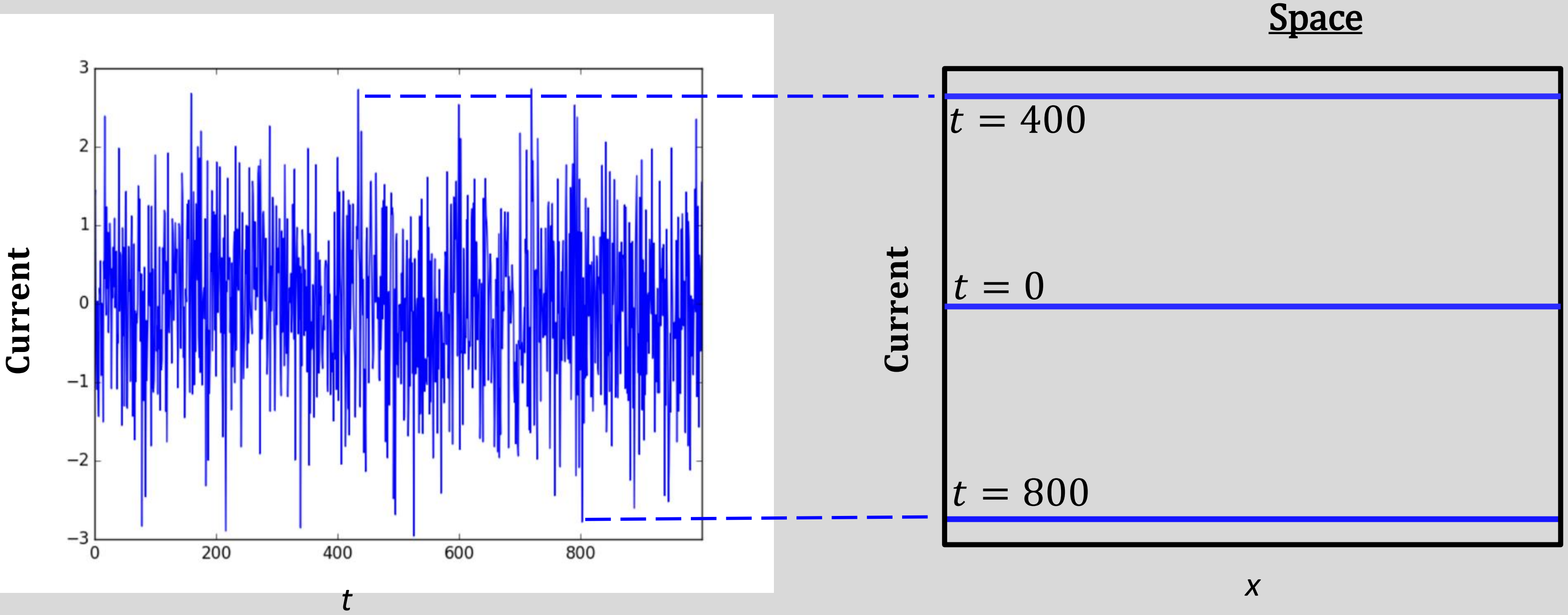
Current Noise J_{total} is Zero in Space

Current Noise
J_{total}
is
HUGE in time

Time

vs

Space



One Dimensional Systems like Channels or Circuit Components

EQUALITY of Total Current J_{total}
is
an Enormous Simplification

It can create a *Perfect Low Pass Filter*

It can *Convert*

***Chaos* of Brownian Motion**

into a *Constant*

What does this mean for Mathematical Models?

The image of total current flow $\mathbf{J}_{total}$ is very different VERY SMOOTH in space

Total Current $\mathbf{J}_{total}$ does not vary in space so

Spatial Derivatives are not needed to describe total current

But they are needed to describe everything else.

This is not magic

Conservation of Total Current
Says the fields of the Maxwell Equations
Are exactly what are needed to conserve current

Maxwell Equations Guarantee that

Atoms in Series System Move
so
Total Current is Equal

Magnetic and Electric Fields
Move Atoms
EXACTLY THE RIGHT AMOUNT
so total current is conserved

Maxwell Equations Guarantee that

Atomic Motions we see in Simulations Are those needed to Conserve Total Current

In my view, this is the best way to understand atomic motion.

Thinking of charges is a fool's errand
there are charges
with $\gg 10^{23}\,!$ interactions

Thinking of Total Current is MUCH Easier

In my view, this is the best way to understand atomic motion.

Thinking of charges is a fool's errand
When there are 10^{23} charges

Thinking of Total Current is MUCH Easier

Atomic Motions we see in Simulations
Are those needed to Conserve Total Current

Spatial Variable does NOT appear in description of current in a one dimensional channel

How take advantage of this enormous simplication?

Current flow is very smooth in spatial coordinate

Differential equation in x is not needed for J_{total}

$$J_{total} = J + \varepsilon_0\, \partial E/\partial t$$

What does this mean for theory and simulations?

Opportunity to Simplify Algorithms and Codes

perhaps dramatically

Spatial Dependence is Already Known

Only have to average the time dependence

Ma, Li and Liu (2016). arXiv:1605.04886; Ma, Li and Liu (2016). arXiv:1606.03625.

Current flow is very smooth in spatial coordinate
Differential equation in x is not needed for $\mathbf{J} + \varepsilon_0\, \partial E/\partial t$

What does this mean for theory and simulations?

YOU tell me!

Opportunity to Simplify Algorithms and Codes

perhaps dramatically

Spatial Dependence is Already Known
Only have to average the time dependence of particle motion
Ma, Li and Liu (2016). arXiv:1605.04886; Ma, Li and Liu (2016). arXiv:1606.03625.

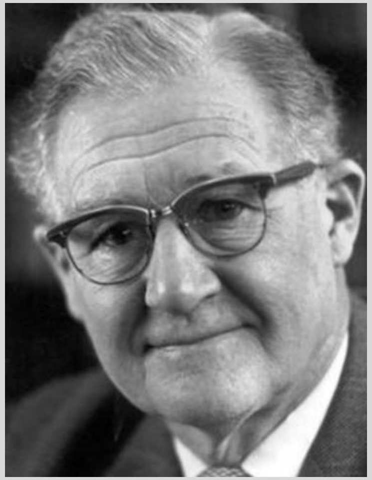
Biophysical Consequences
Of
Perfect Conservation of Total Current

1. Total Current does not hop in Channels
2. Kirchhoff Coupling in NerveSignal
3. Kirchhoff Coupling in Mitochondria and Transporters
4. Kirchhoff Coupling is different in vesicles/mitochondria, and in voltage clamped bilayers.

Some Biologists Know How to Use the Maxwell Equations

Some biologists have been Applying Maxwell to the Nerve Signal for a long time

Alan Hodgkin



William Rushton

Proc Roy Soc (London) Ser B. 1946;133:444-79.

Channels are Chemically and Structurally INDEPENDENT

Electric Field Couples Channels so they can make a Useful Electrical Signal, the Action Potential

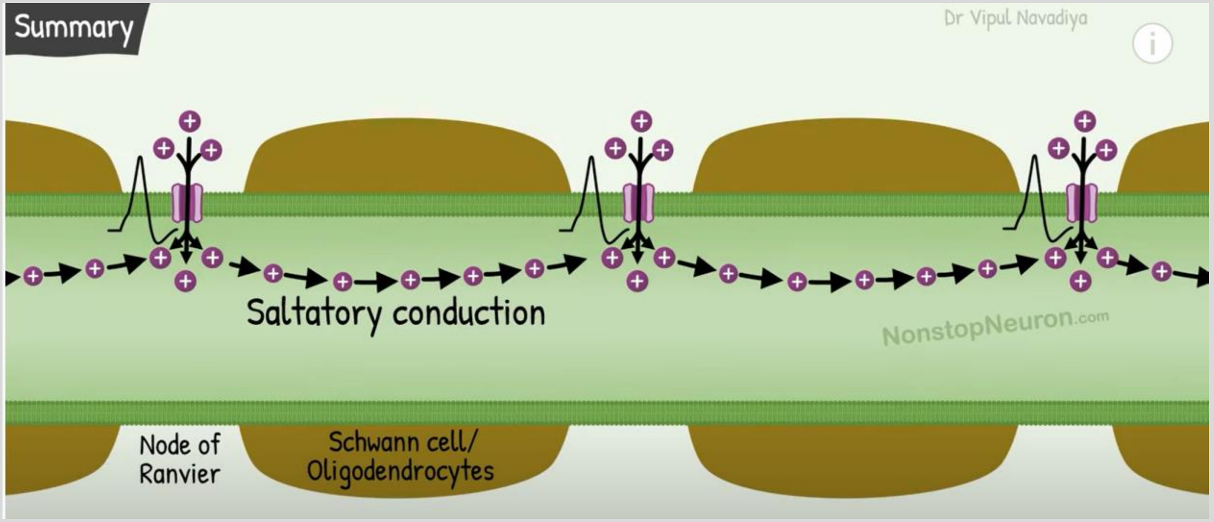
Channels are Chemically and Structurally INDEPENDENT

Natural Function of Channels Requires Coupling by the Electric Field

Electric Field Couples Channels
so they can make a
Useful Electrical Signal
the Action Potential

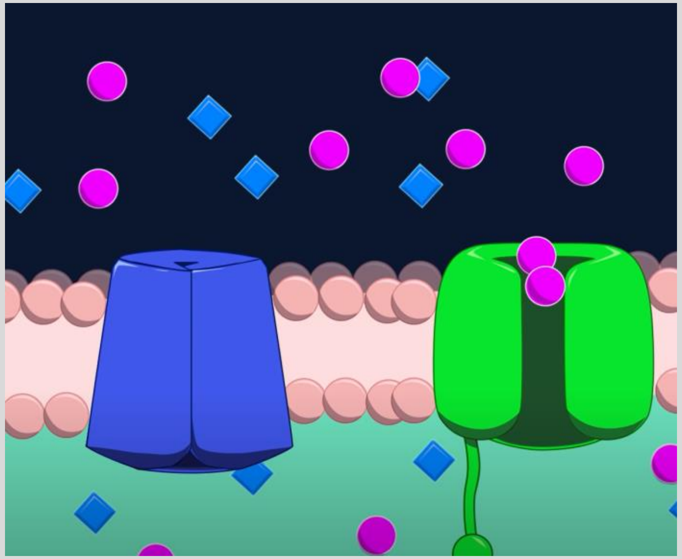
Coupling in Natural Function is by Electric Field, i.e., VOLTAGE SPREAD

Nerve Fiber with Myelin



https://www.youtube.com/watch?v=tOTYO5WrXFU

Channels

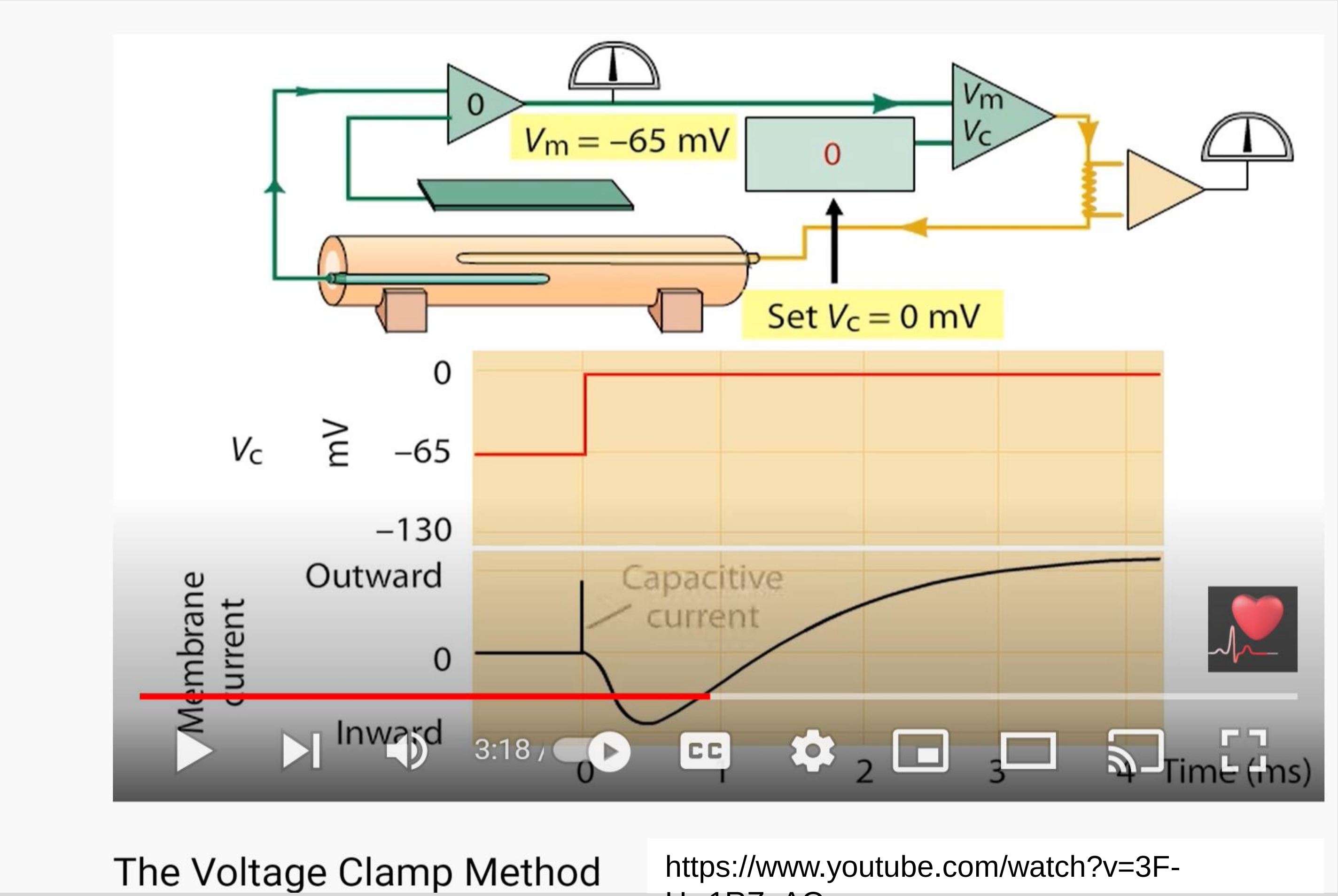


Na **K**

https://www.youtube.com/watch?v=oa6rvUJlg7o

ONLY in the Unnatural Voltage Clamp are Channels Independent

Huxley **Hodgkin**



The Voltage Clamp Method

https://www.youtube.com/watch?v=3F-Uw1RZqAQ

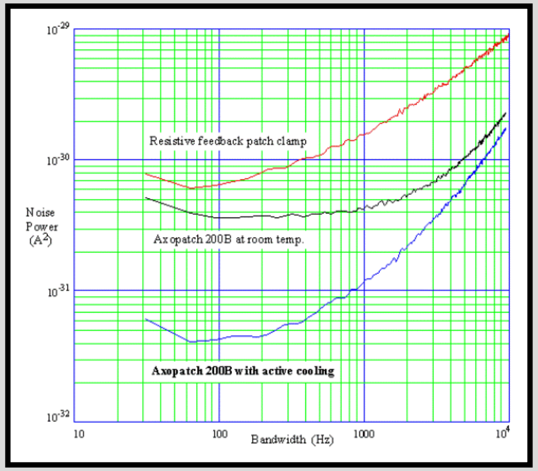
KS Cole

Our Axopatch makes Voltage Clamp seem natural

It is not.

UNclamp is Natural!

AxoPatch 200B



Ion channel newsletter

Ion Channel Monthly

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Popular publications for March (view most recent)

1. Molecular basis of infrared detection by snakes. *Nature*
2. The Angelman Syndrome Protein Ube3A Regulates Synapse Development by Ubiquitinating Arc. *Cell*
3. AMPA receptors--another twist? *Science*
4. Molecular Basis of Calcium Signaling in Lymphocytes: STIM and ORAI. *Annu Rev Immunol*
5. Neurological Channelopathies. *Annu Rev Neurosci*
6. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet*
7. A Glial Signal Consisting of Gliomedin and NrCAM Clusters Axonal Na(+) Channels during the Formation of Nodes of Ranvier. *Neuron*
8. Small Molecule Activators of TRPML3. *Chem Biol*
9. Truncated {beta}-amyloid peptide channels provide an alternative mechanism for Alzheimer's Disease and Down syndrome. *Proc Natl Acad Sci U S A*
10. Modelling the molecular mechanisms of synaptic plasticity using systems biology approaches. *Nat Rev Neurosci*
11. Pathophysiological roles of transient receptor potential channels in glial cells. *Yakugaku Zasshi*
12. Targeted Delivery of siRNA to Macrophages for Anti-inflammatory Treatment. *Mol Ther*
13. Guard Cell Signal Transduction Network: Advances in

Sponsors:

- Bsys - Swiss Quality in Ion Channel Services
- Automate Scientific - Electrophysiology Equipment
- Cellectricon - Dynaflow: a quantum leap for electrophysiology
- Nanion - Automated patch clamp
- Millipore - Ion channel cell lines

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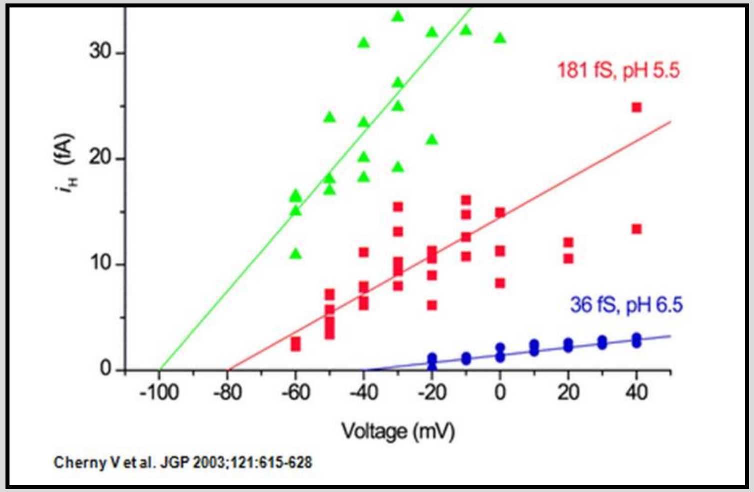
Upcoming Events:

- 2010 Ion Channel Retreat



Cherny V et al. JGP 2003;121:615-628

Important Applications
in Biology and Technology

What are the PHYSICAL problems with traditional Maxwell Equations?

Classical Maxwell's equations do not deal with
Diffusion
Convection
Complex materials
Complicated dielectric properties

Indeed, Maxwell's original equations do not include ions or electrons or their movement!
Textbook treatments do not deal with other forces like diffusion or convection at all.

Eisenberg, 2019. **Dielectric Dilemma**. arXxiv: 1901.10805.

Traditional Form of Maxwell Equations Cannot be Used

Maxwell's equations do not deal with

Diffusion

Convection

Complex materials

Complex dielectric properties*
present in almost all materials

*Eisenberg, 2019. Dielectric Dilemma. arXiv: 1901.10805.

It is necessary to update Maxwell's Equations

https://arxiv.org/abs/1904.09695

Not just my opinion

This is the opinion* of Nobel Prize winners in Physics,

Richard Feynman

(quantum electrodynamics)

and

Edward Purcell

(nuclear magnetic resonance)

*p. 10-7 of Feynman, Leighton, and Sands. 1963. ***Mainly Electromagnetism and Matter***

*****p. 506 of Purcell and Morin. 2013. ***Electricity and Magnetism***

It is necessary (and feasible) **to update Maxwell's Equations**

https://arxiv.org/abs/1904.09695

Work in Progress!!!

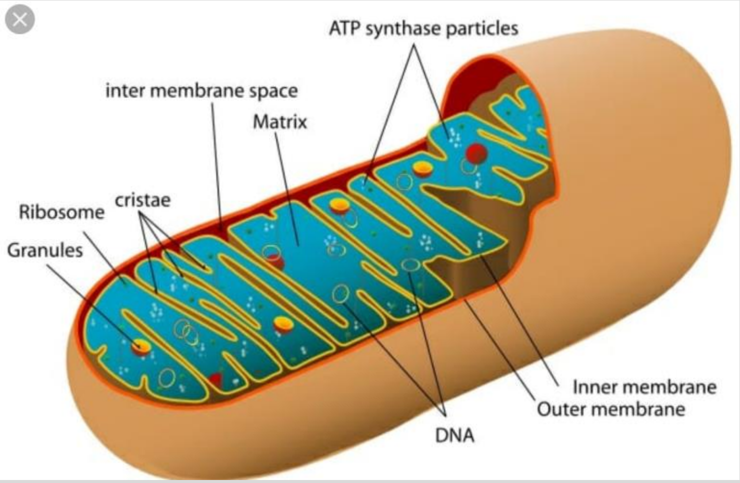
Eisenberg, B., C. Liu and Y. Wang (2022). "On Variational Principles for Polarization Responses in Electromechanical Systems." Communications in Mathematical Sciences 20(6): 1541-1550.

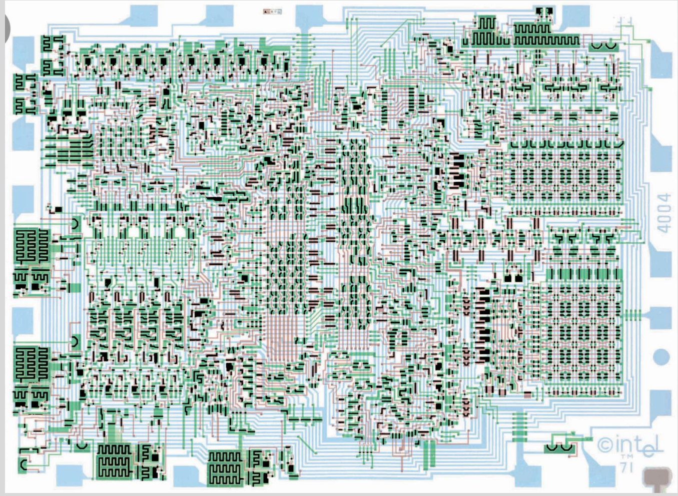
Wang, Y., C. Liu, P. Liu and B. Eisenberg (2020). "Field theory of reaction-diffusion: Law of mass action with an energetic variational approach." Physical Review E 102(6): 062147 Preprint available on the physics arXiv at https://arxiv.org/abs/062001.010149.

Xu, S., R. Eisenberg, Z. Song and H. Huang (2022). "Mathematical Model for Chemical Reactions in Electrolyte Applied to Cytochrome $ c $ Oxidase: an Electro-osmotic Approach." arXiv preprint arXiv:2207.02215.

Kirchhoff's Current Law
is the key
that allows predictions
in Biophysics and Engineering

Equivalent to the Maxwell Equations themselves





Valid at 10^{-10} sec and 10^{-8} cm

From Maxwell
to
Mitochondria

Seems Hopeless

$\mathbf{10^{17}}$ **charges**

$\mathbf{10^{17}}$**factorial pairwise interactions** $\cong \left(\mathbf{10^{17}}\right)^{\mathbf{10^{17}}} \times \left(\sqrt{\mathbf{2\pi 10^{17}}/e^{\mathbf{10^{17}}}}\right)$

From Maxwell
to
Integrated Circuits

is obvious
to Engineers

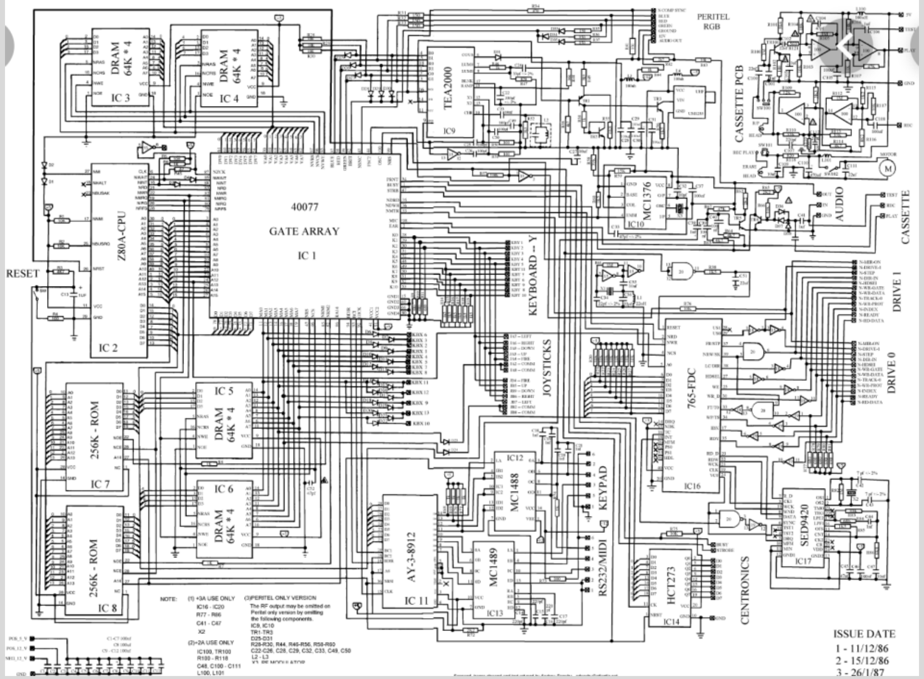
10^{17} charges

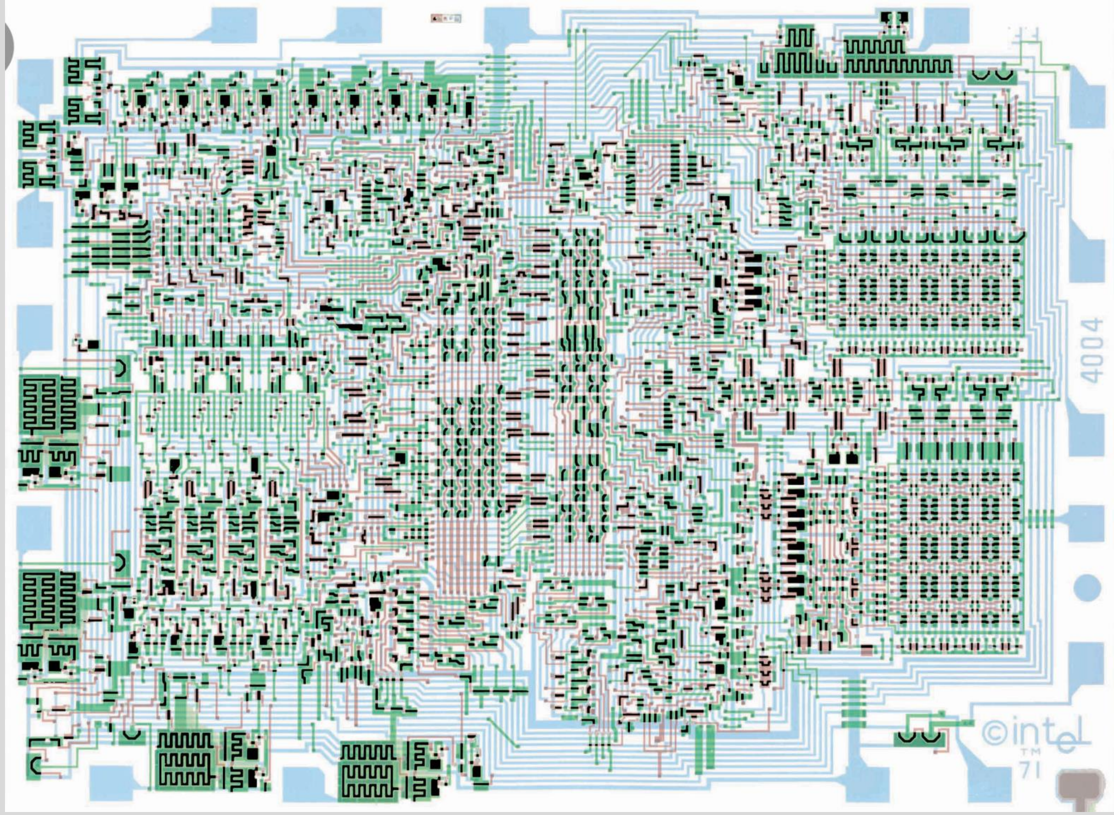
10^{17}factorial pairwise interactions

Is it

Hopeless to know all charges and how they move in an IC?

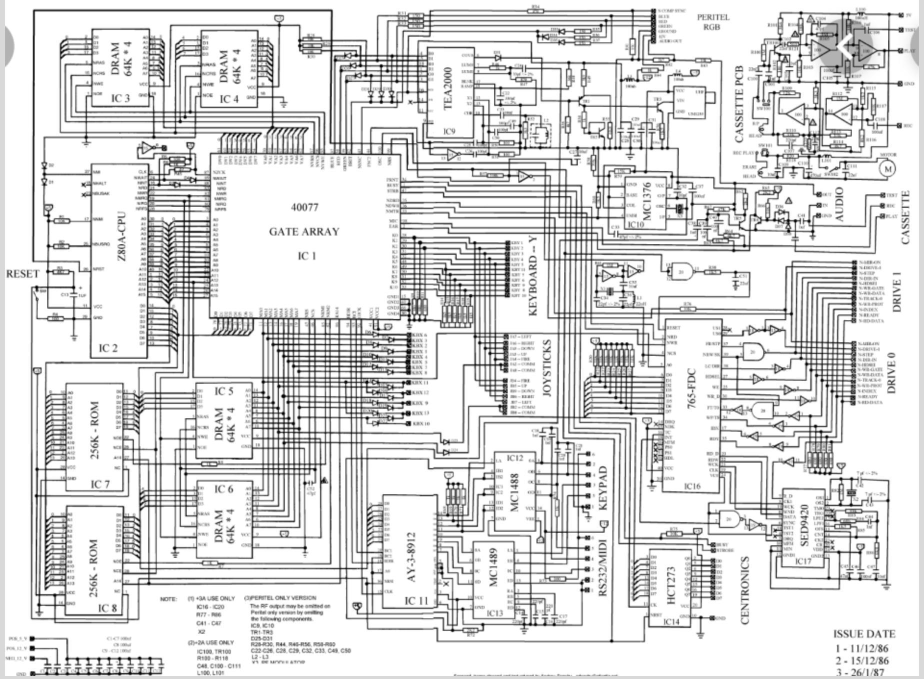
integrated circuit





10^{17} charges

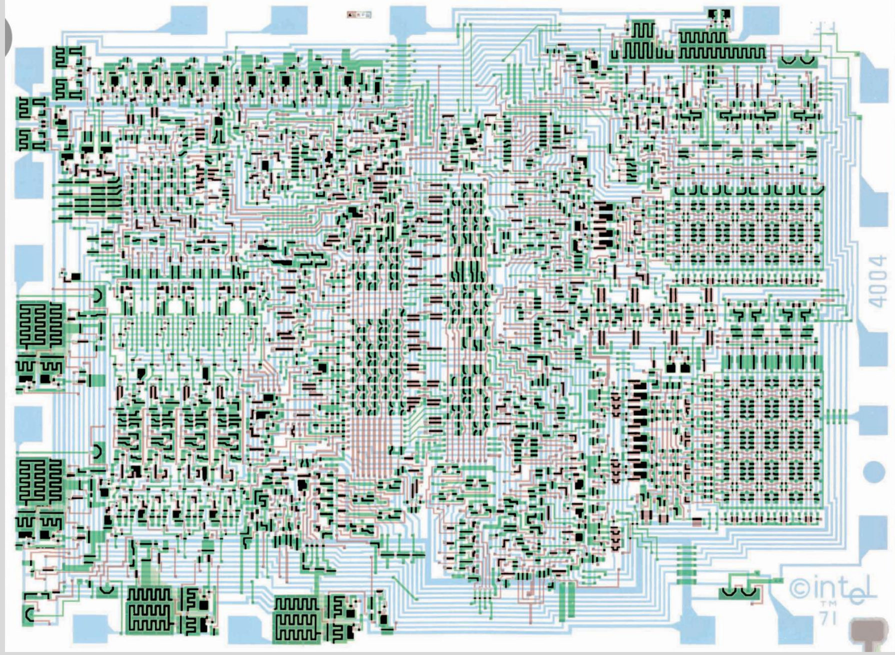
10^{17}factorial pairwise interactions



Fortunately,

It is NOT necessary in our computers to know all the charges!

Kirchhoff's law is (almost) **enough**



Conservation of Current

makes

Analysis Possible

In Complex Biological Systems

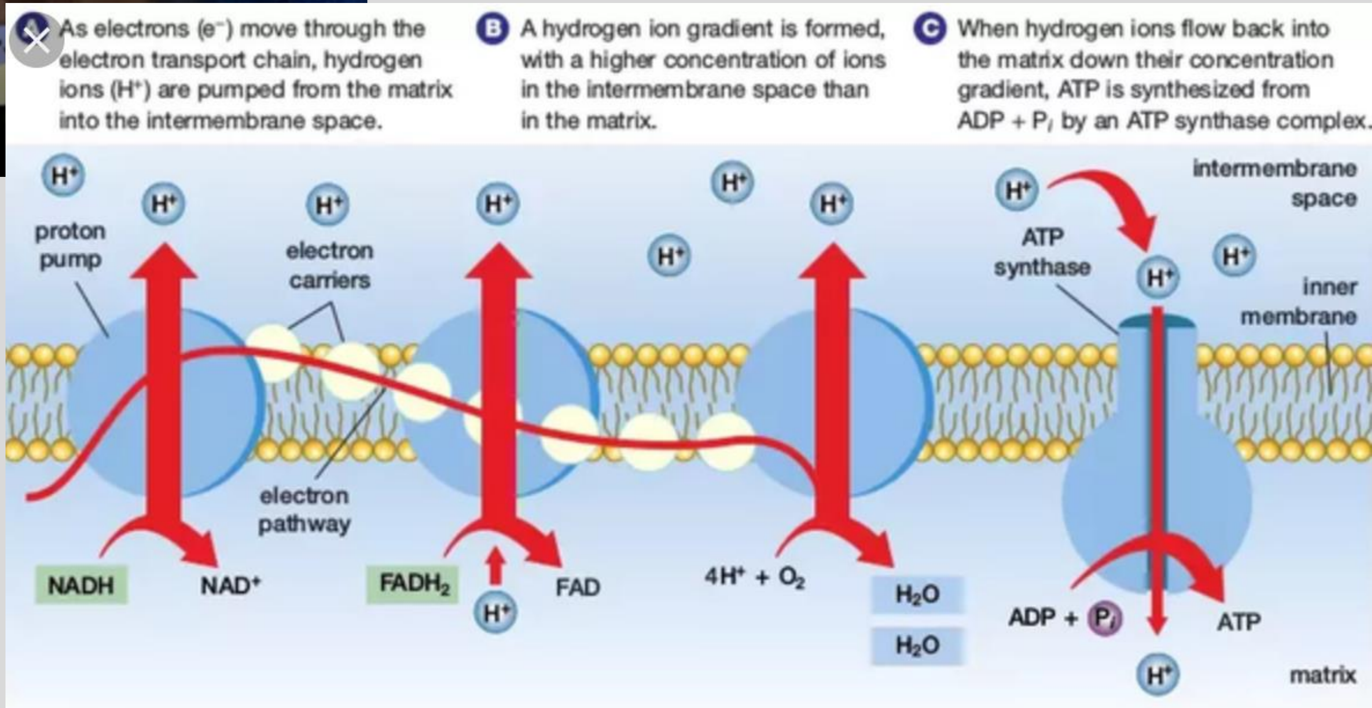
and

Complex Engineering Systems

we do NOT have to know all ~10^{17} charges
and how they interact or move

Mitochondrion

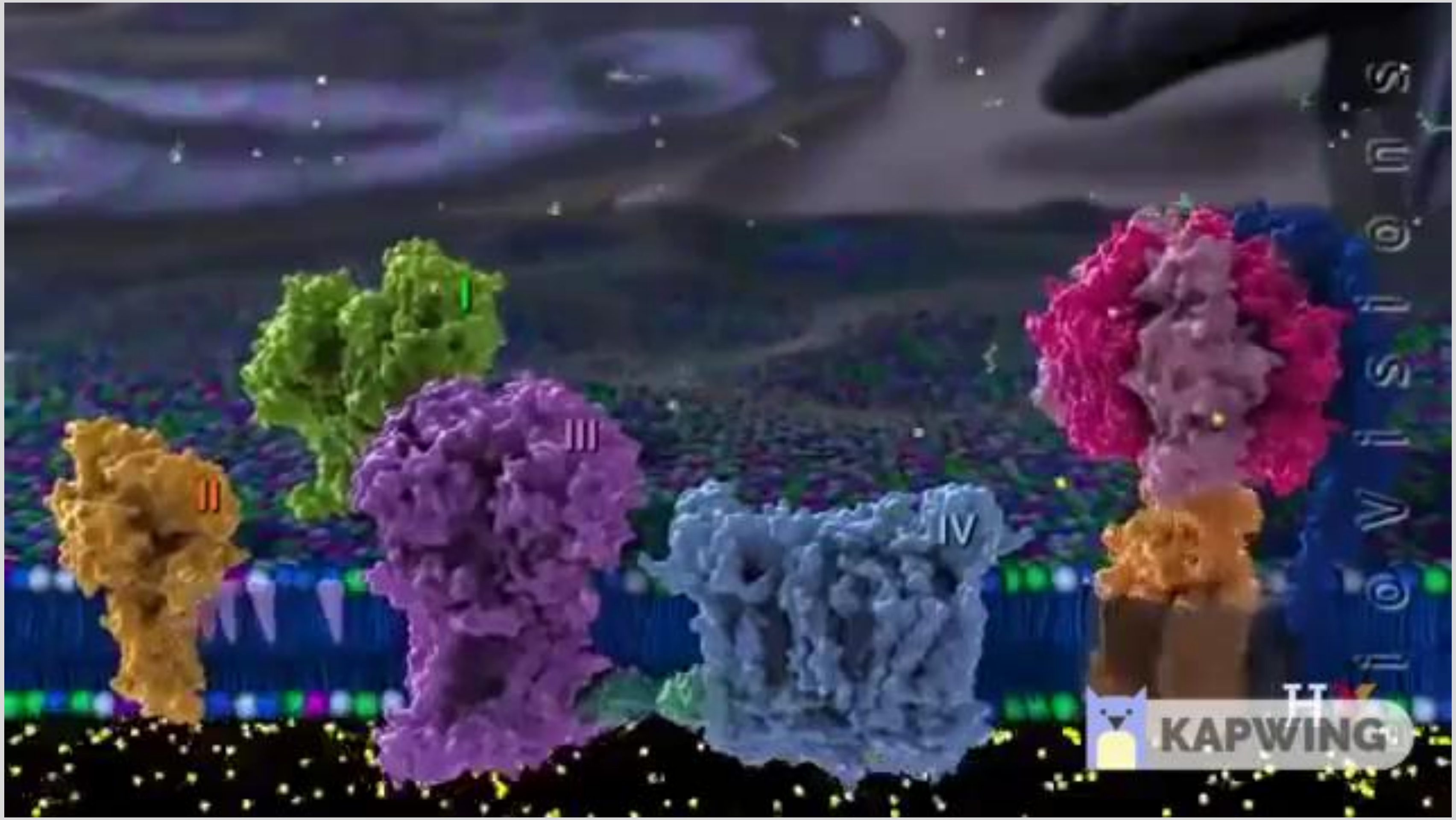
Applying Maxwell To Mitochondrion Depends on Conservation of Current



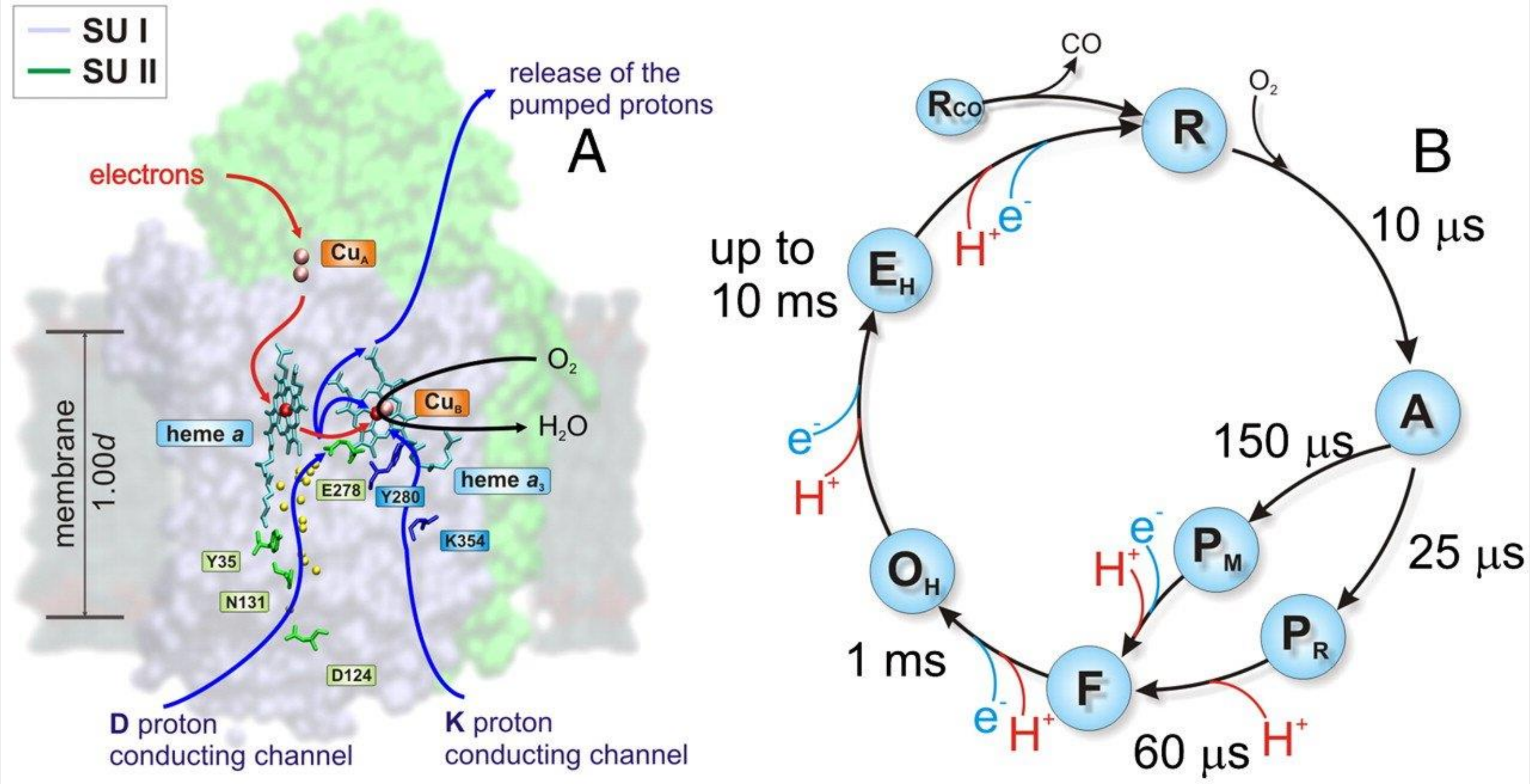
A As electrons (e⁻) move through the electron transport chain, hydrogen ions (H^+) are pumped from the matrix into the intermembrane space.

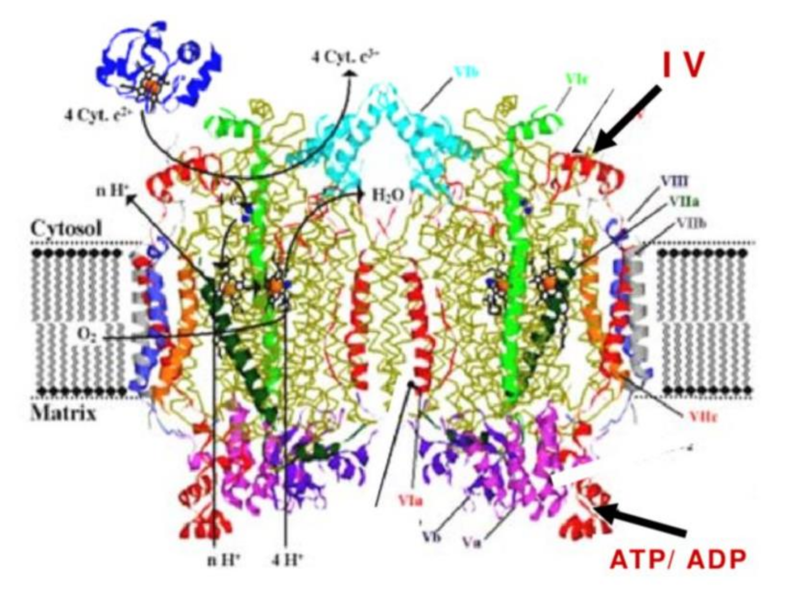
B A hydrogen ion gradient is formed, with a higher concentration of ions in the intermembrane space than in the matrix.

C When hydrogen ions flow back into the matrix down their concentration gradient, ATP is synthesized from ADP + P_i by an ATP synthase complex.


I
II
III
IV

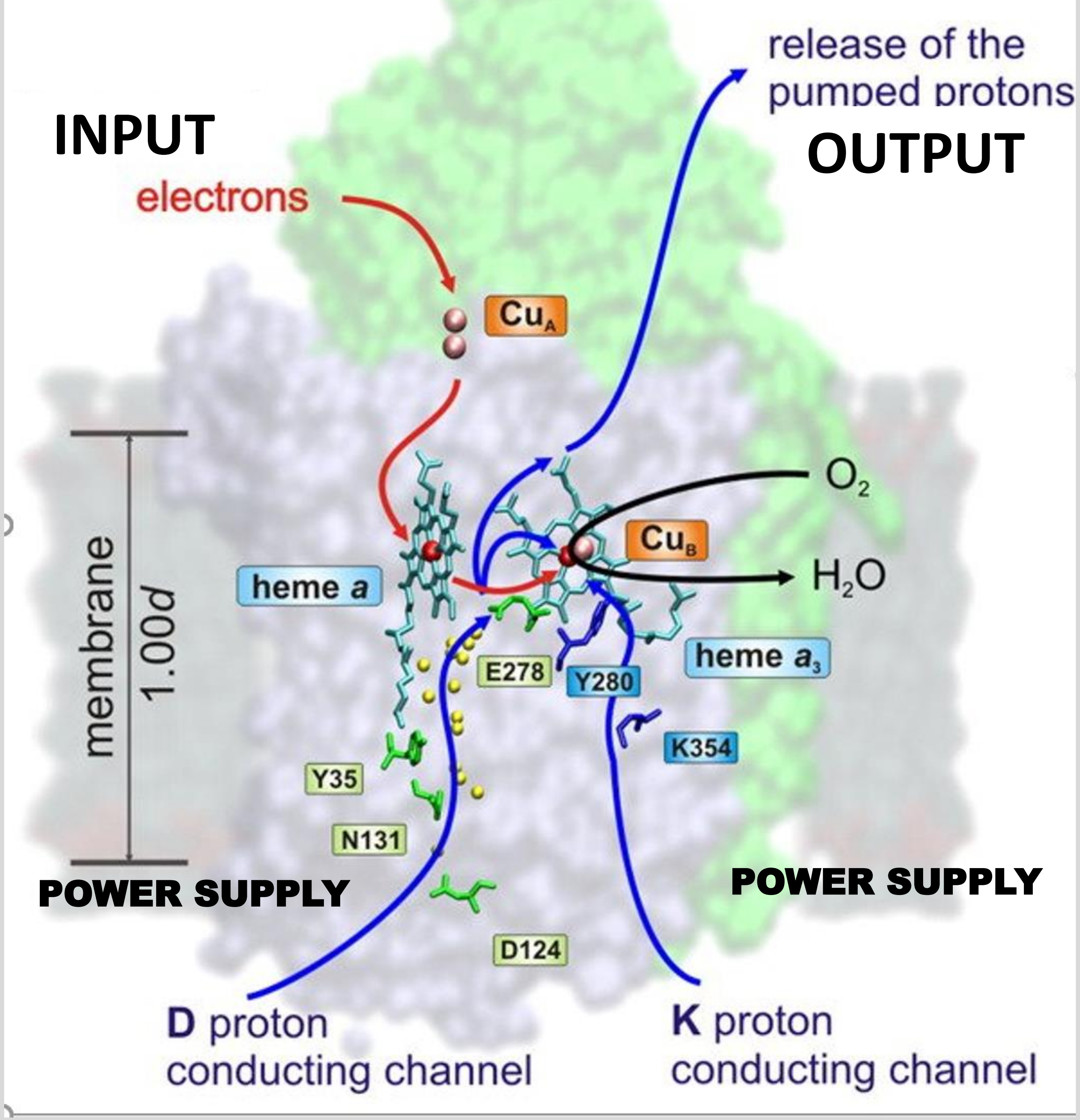
Cytochrome c oxidase
Complex IV





Magdalena Misiak National Institute on Aging

Belevich et al, PNAS 2010;107:18469



INPUT

OUTPUT

POWER SUPPLY

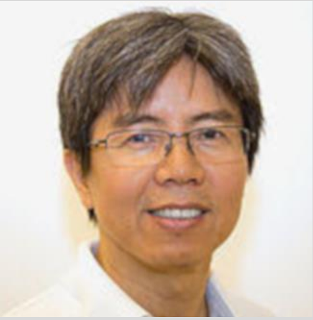
POWER SUPPLY

Circuit Model of Cytochrome Oxidase C

Shixin Xu

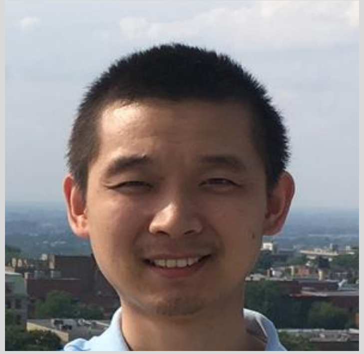
士鑫 徐

Project Leader



Huaxiong Huang

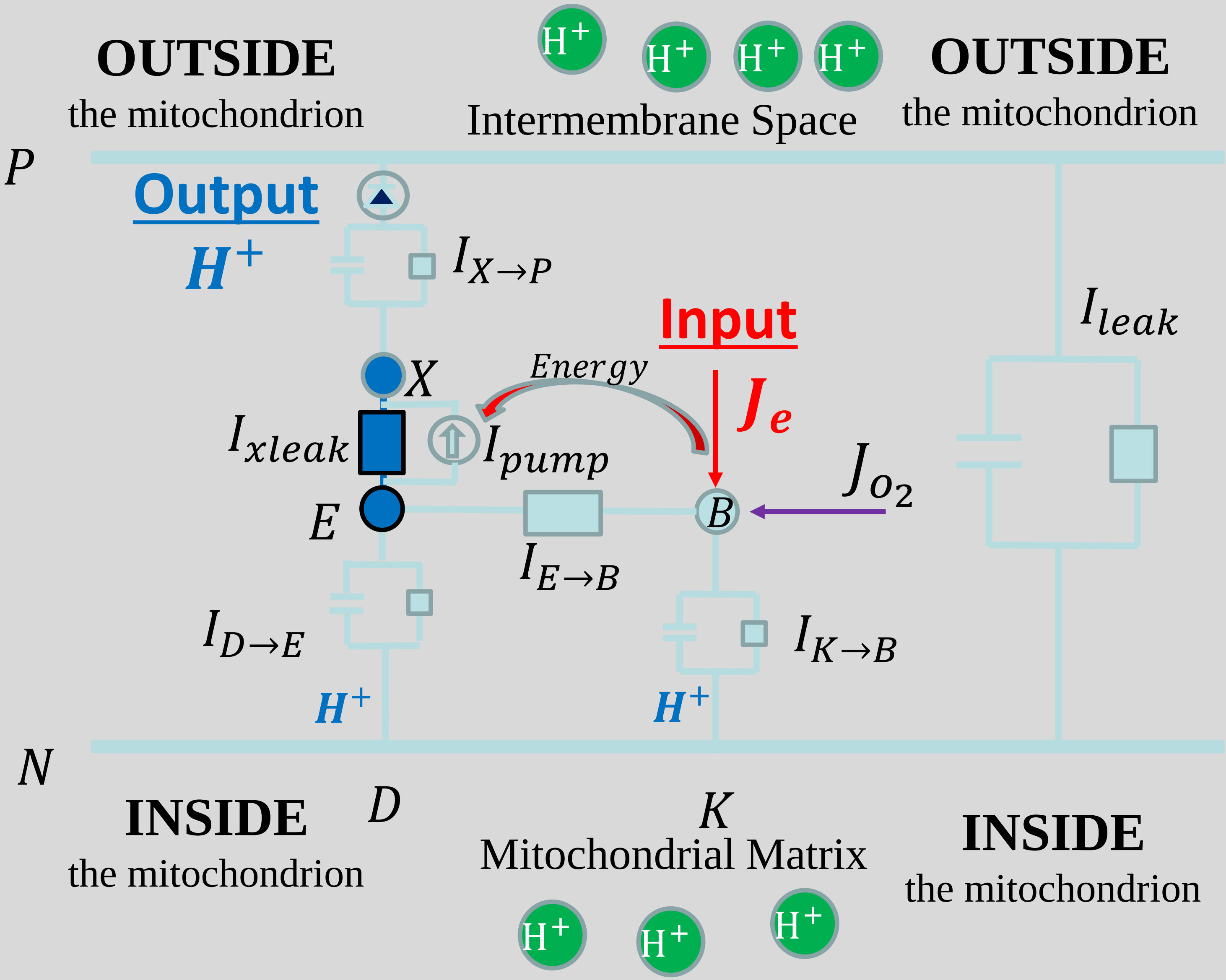
华雄 **黄**



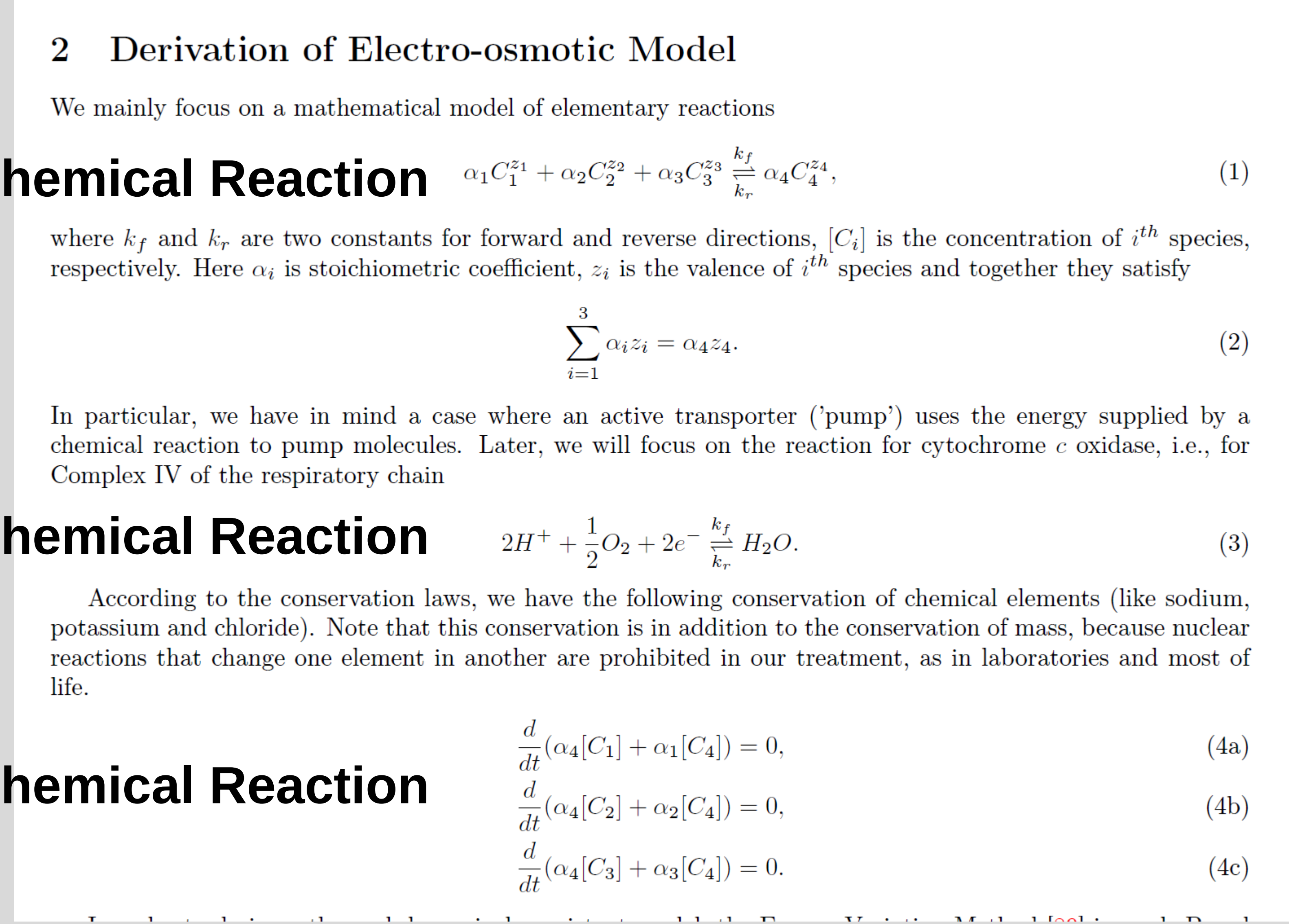
Zilong Song

宋子龙

Circuit Model
of Cytochrome Oxidase C



Our Representation Without detailed reaction timings



2 Derivation of Electro-osmotic Model

We mainly focus on a mathematical model of elementary reactions

Chemical Reaction

$$\alpha_1 C_1^{z_1} + \alpha_2 C_2^{z_2} + \alpha_3 C_3^{z_3} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \alpha_4 C_4^{z_4}, \tag{1}$$

where k_f and k_r are two constants for forward and reverse directions, $[C_i]$ is the concentration of i^{th} species, respectively. Here α_i is stoichiometric coefficient, z_i is the valence of i^{th} species and together they satisfy

$$\sum_{i=1}^{3} \alpha_i z_i = \alpha_4 z_4. \tag{2}$$

In particular, we have in mind a case where an active transporter ('pump') uses the energy supplied by a chemical reaction to pump molecules. Later, we will focus on the reaction for cytochrome c oxidase, i.e., for Complex IV of the respiratory chain

Chemical Reaction

$$2H^+ + \frac{1}{2}O_2 + 2e^- \underset{k_r}{\overset{k_f}{\rightleftharpoons}} H_2O. \tag{3}$$

According to the conservation laws, we have the following conservation of chemical elements (like sodium, potassium and chloride). Note that this conservation is in addition to the conservation of mass, because nuclear reactions that change one element in another are prohibited in our treatment, as in laboratories and most of life.

Chemical Reaction

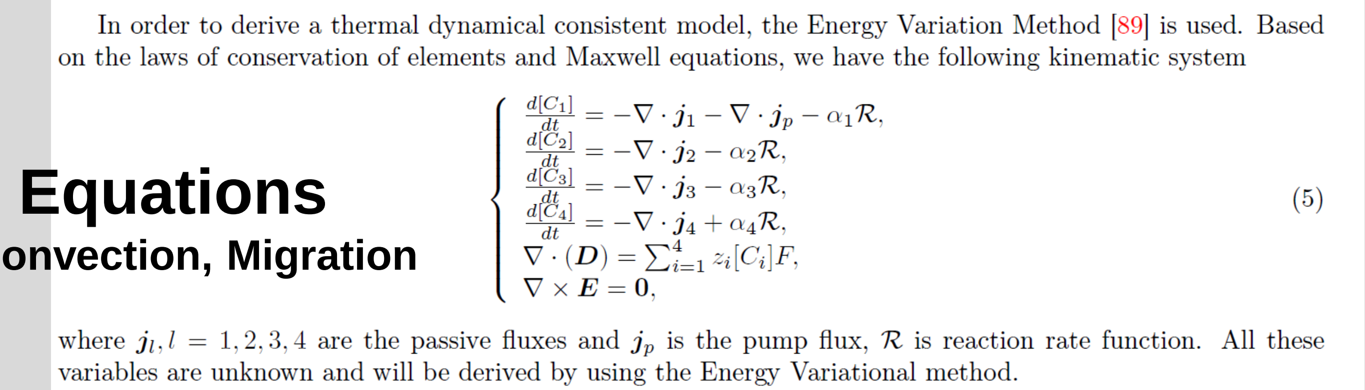
$$\frac{d}{dt}(\alpha_4[C_1] + \alpha_1[C_4]) = 0, \tag{4a}$$

$$\frac{d}{dt}(\alpha_4[C_2] + \alpha_2[C_4]) = 0, \tag{4b}$$

$$\frac{d}{dt}(\alpha_4[C_3] + \alpha_3[C_4]) = 0. \tag{4c}$$

Field Equations

Diffusion, Convection, Migration



In order to derive a thermal dynamical consistent model, the Energy Variation Method [89] is used. Based on the laws of conservation of elements and Maxwell equations, we have the following kinematic system

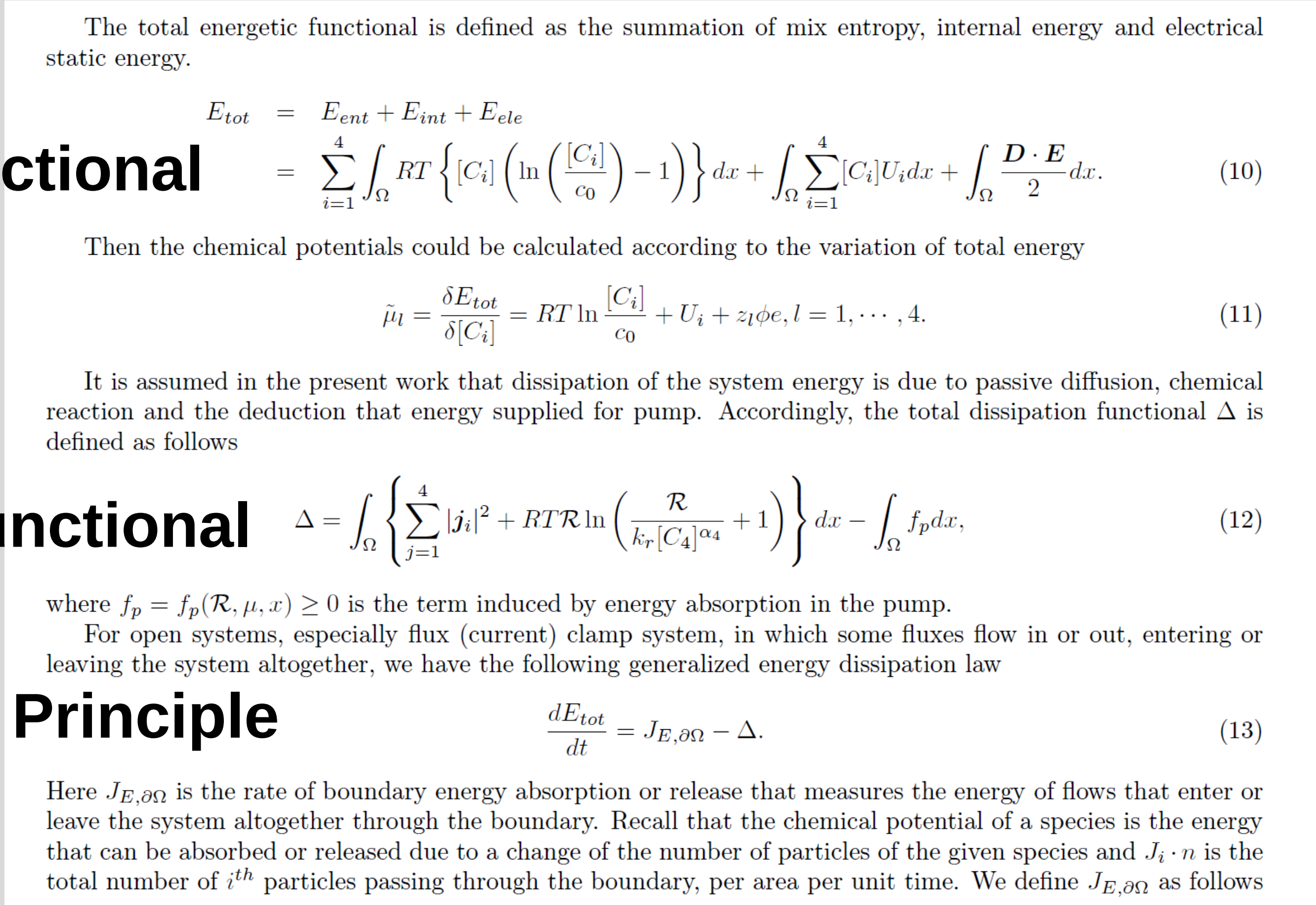
$$\begin{cases} \frac{d[C_1]}{dt} = -\nabla\cdot\boldsymbol{j}_1 - \nabla\cdot\boldsymbol{j}_p - \alpha_1\mathcal{R}, \\ \frac{d[C_2]}{dt} = -\nabla\cdot\boldsymbol{j}_2 - \alpha_2\mathcal{R}, \\ \frac{d[C_3]}{dt} = -\nabla\cdot\boldsymbol{j}_3 - \alpha_3\mathcal{R}, \\ \frac{d[C_4]}{dt} = -\nabla\cdot\boldsymbol{j}_4 + \alpha_4\mathcal{R}, \\ \nabla\cdot(\boldsymbol{D}) = \sum_{i=1}^{4} z_i[C_i]F, \\ \nabla\times\boldsymbol{E} = \boldsymbol{0}, \end{cases} \tag{5}$$

where $\boldsymbol{j}_l, l = 1,2,3,4$ are the passive fluxes and $\boldsymbol{j}_p$ is the pump flux, $\mathcal{R}$ is reaction rate function. All these variables are unknown and will be derived by using the Energy Variational method.

Energy Functional

Dissipation Functional

Dissipation Principle



The total energetic functional is defined as the summation of mix entropy, internal energy and electrical static energy.

$$\begin{aligned} E_{tot} &= E_{ent} + E_{int} + E_{ele} \\ &= \sum_{i=1}^{4}\int_\Omega RT\left\{[C_i]\left(\ln\left(\frac{[C_i]}{c_0}\right) - 1\right)\right\}dx + \int_\Omega \sum_{i=1}^{4}[C_i]U_i dx + \int_\Omega \frac{\boldsymbol{D}\cdot\boldsymbol{E}}{2}dx. \end{aligned} \tag{10}$$

Then the chemical potentials could be calculated according to the variation of total energy

$$\tilde{\mu}_l = \frac{\delta E_{tot}}{\delta[C_i]} = RT\ln\frac{[C_i]}{c_0} + U_i + z_l\phi e, l = 1,\cdots,4. \tag{11}$$

It is assumed in the present work that dissipation of the system energy is due to passive diffusion, chemical reaction and the deduction that energy supplied for pump. Accordingly, the total dissipation functional Δ is defined as follows

$$\Delta = \int_\Omega \left\{\sum_{j=1}^{4}|\boldsymbol{j}_i|^2 + RT\mathcal{R}\ln\left(\frac{\mathcal{R}}{k_r[C_4]^{\alpha_4}} + 1\right)\right\}dx - \int_\Omega f_p dx, \tag{12}$$

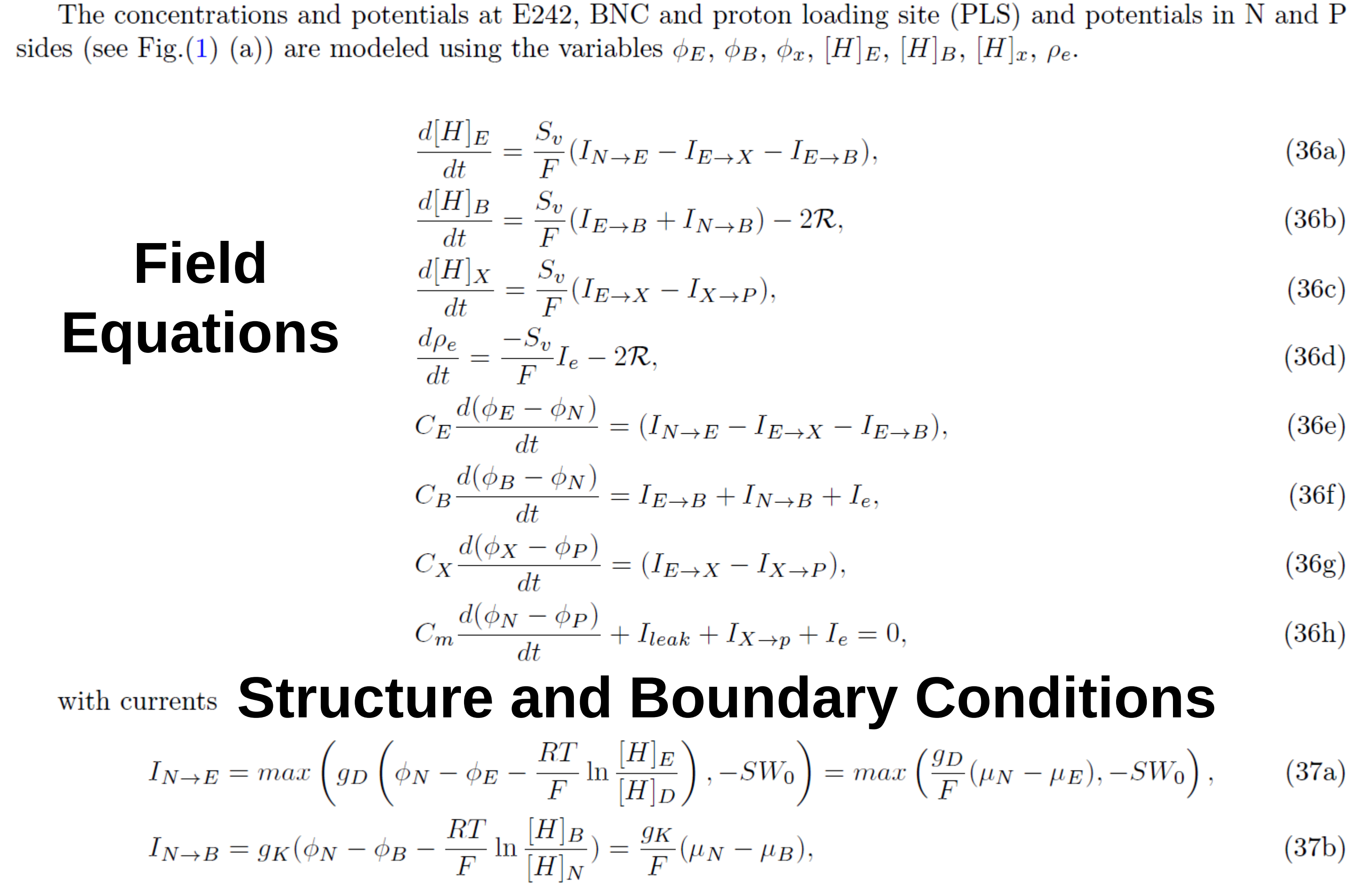
where $f_p = f_p(\mathcal{R},\mu,x) \geq 0$ is the term induced by energy absorption in the pump.

For open systems, especially flux (current) clamp system, in which some fluxes flow in or out, entering or leaving the system altogether, we have the following generalized energy dissipation law

$$\frac{dE_{tot}}{dt} = J_{E,\partial\Omega} - \Delta. \tag{13}$$

Here $J_{E,\partial\Omega}$ is the rate of boundary energy absorption or release that measures the energy of flows that enter or leave the system altogether through the boundary. Recall that the chemical potential of a species is the energy that can be absorbed or released due to a change of the number of particles of the given species and $J_i\cdot n$ is the total number of i^{th} particles passing through the boundary, per area per unit time. We define $J_{E,\partial\Omega}$ as follows

An Electro-osmotic Model of cytochrome c oxidase



The concentrations and potentials at E242, BNC and proton loading site (PLS) and potentials in N and P sides (see Fig.(1) (a)) are modeled using the variables ϕ_E, ϕ_B, ϕ_x, $[H]_E$, $[H]_B$, $[H]_x$, ρ_e.

Field Equations

$$\frac{d[H]_E}{dt} = \frac{S_v}{F}(I_{N\to E} - I_{E\to X} - I_{E\to B}), \tag{36a}$$

$$\frac{d[H]_B}{dt} = \frac{S_v}{F}(I_{E\to B} + I_{N\to B}) - 2\mathcal{R}, \tag{36b}$$

$$\frac{d[H]_X}{dt} = \frac{S_v}{F}(I_{E\to X} - I_{X\to P}), \tag{36c}$$

$$\frac{d\rho_e}{dt} = \frac{-S_v}{F} I_e - 2\mathcal{R}, \tag{36d}$$

$$C_E \frac{d(\phi_E - \phi_N)}{dt} = (I_{N\to E} - I_{E\to X} - I_{E\to B}), \tag{36e}$$

$$C_B \frac{d(\phi_B - \phi_N)}{dt} = I_{E\to B} + I_{N\to B} + I_e, \tag{36f}$$

$$C_X \frac{d(\phi_X - \phi_P)}{dt} = (I_{E\to X} - I_{X\to P}), \tag{36g}$$

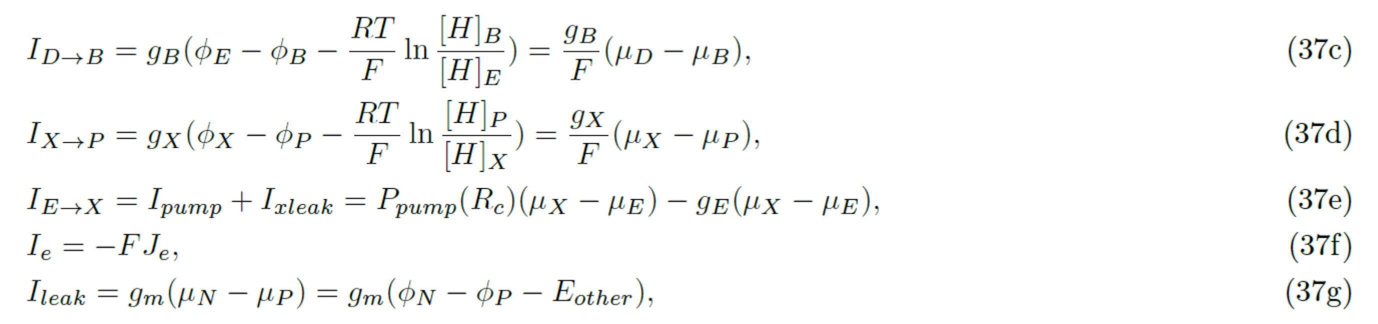
$$C_m \frac{d(\phi_N - \phi_P)}{dt} + I_{leak} + I_{X\to p} + I_e = 0, \tag{36h}$$

with currents **Structure and Boundary Conditions**

$$I_{N\to E} = max\left(g_D\left(\phi_N - \phi_E - \frac{RT}{F}\ln\frac{[H]_E}{[H]_D}\right), -SW_0\right) = max\left(\frac{g_D}{F}(\mu_N - \mu_E), -SW_0\right), \tag{37a}$$

$$I_{N\to B} = g_K(\phi_N - \phi_B - \frac{RT}{F}\ln\frac{[H]_B}{[H]_N}) = \frac{g_K}{F}(\mu_N - \mu_B), \tag{37b}$$

More Structure and Boundary Conditions



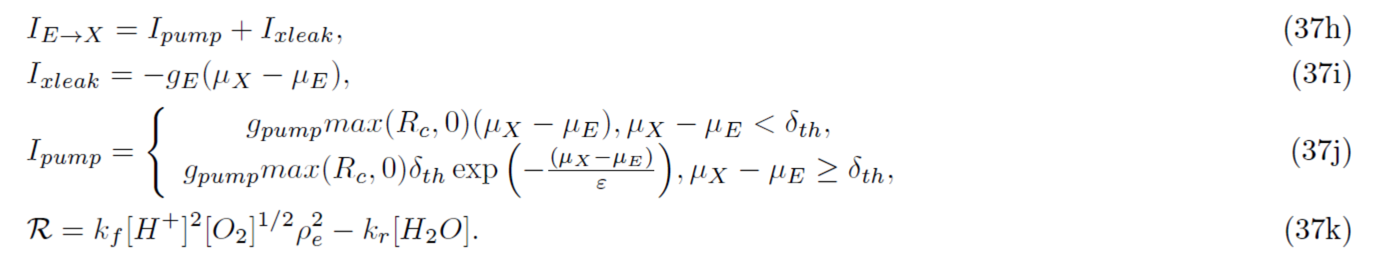
$$I_{D\rightarrow B} = g_B(\phi_E - \phi_B - \frac{RT}{F}\ln\frac{[H]_B}{[H]_E}) = \frac{g_B}{F}(\mu_D - \mu_B), \tag{37c}$$

$$I_{X\rightarrow P} = g_X(\phi_X - \phi_P - \frac{RT}{F}\ln\frac{[H]_P}{[H]_X}) = \frac{g_X}{F}(\mu_X - \mu_P), \tag{37d}$$

$$I_{E\rightarrow X} = I_{pump} + I_{xleak} = P_{pump}(R_c)(\mu_X - \mu_E) - g_E(\mu_X - \mu_E), \tag{37e}$$

$$I_e = -FJ_e, \tag{37f}$$

$$I_{leak} = g_m(\mu_N - \mu_P) = g_m(\phi_N - \phi_P - E_{other}), \tag{37g}$$



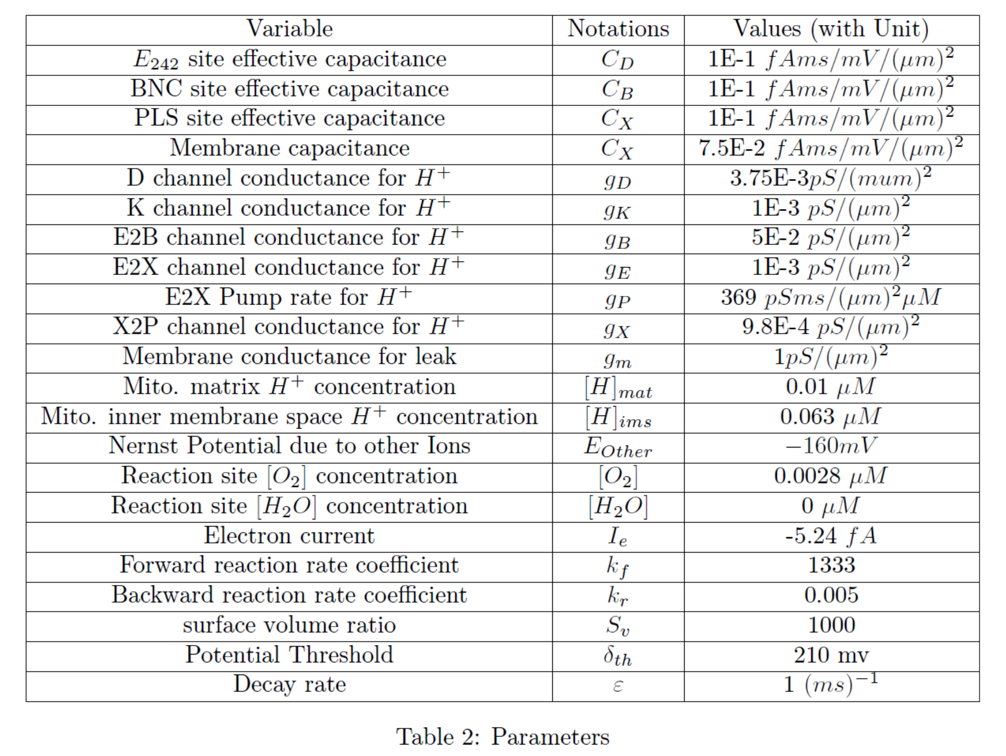
$$I_{E\rightarrow X} = I_{pump} + I_{xleak}, \tag{37h}$$

$$I_{xleak} = -g_E(\mu_X - \mu_E), \tag{37i}$$

$$I_{pump} = \begin{cases} g_{pump}max(R_c, 0)(\mu_X - \mu_E), \mu_X - \mu_E < \delta_{th}, \\ g_{pump}max(R_c, 0)\delta_{th}\exp\left(-\frac{(\mu_X - \mu_E)}{\varepsilon}\right), \mu_X - \mu_E \geq \delta_{th}, \end{cases} \tag{37j}$$

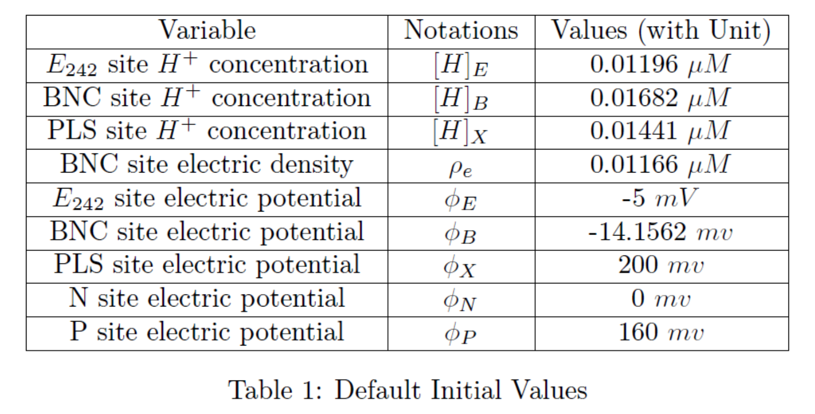
$$\mathcal{R} = k_f[H^+]^2[O_2]^{1/2}\rho_e^2 - k_r[H_2O]. \tag{37k}$$

Preliminary Parameter Values



Variable	Notations	Values (with Unit)
E_{242} site effective capacitance	C_D	1E-1 $fAms/mV/(\mu m)^2$
BNC site effective capacitance	C_B	1E-1 $fAms/mV/(\mu m)^2$
PLS site effective capacitance	C_X	1E-1 $fAms/mV/(\mu m)^2$
Membrane capacitance	C_X	7.5E-2 $fAms/mV/(\mu m)^2$
D channel conductance for H^+	g_D	3.75E-3$pS/(mum)^2$
K channel conductance for H^+	g_K	1E-3 $pS/(\mu m)^2$
E2B channel conductance for H^+	g_B	5E-2 $pS/(\mu m)^2$
E2X channel conductance for H^+	g_E	1E-3 $pS/(\mu m)^2$
E2X Pump rate for H^+	g_P	369 $pSms/(\mu m)^2\mu M$
X2P channel conductance for H^+	g_X	9.8E-4 $pS/(\mu m)^2$
Membrane conductance for leak	g_m	1$pS/(\mu m)^2$
Mito. matrix H^+ concentration	$[H]_{mat}$	0.01 μM
Mito. inner membrane space H^+ concentration	$[H]_{ims}$	0.063 μM
Nernst Potential due to other Ions	E_{Other}	$-160mV$
Reaction site $[O_2]$ concentration	$[O_2]$	0.0028 μM
Reaction site $[H_2O]$ concentration	$[H_2O]$	0 μM
Electron current	I_e	-5.24 fA
Forward reaction rate coefficient	k_f	1333
Backward reaction rate coefficient	k_r	0.005
surface volume ratio	S_v	1000
Potential Threshold	δ_{th}	210 mv
Decay rate	ε	1 $(ms)^{-1}$

Table 2: Parameters



Variable	Notations	Values (with Unit)
E_{242} site H^+ concentration	$[H]_E$	0.01196 μM
BNC site H^+ concentration	$[H]_B$	0.01682 μM
PLS site H^+ concentration	$[H]_X$	0.01441 μM
BNC site electric density	ρ_e	0.01166 μM
E_{242} site electric potential	ϕ_E	-5 mV
BNC site electric potential	ϕ_B	-14.1562 mv
PLS site electric potential	ϕ_X	200 mv
N site electric potential	ϕ_N	0 mv
P site electric potential	ϕ_P	160 mv

Table 1: Default Initial Values

Early Results

Everything can be Computed.

Model can be modified to deal with other information and predict experiments

Not yet digested!

Clamping the Voltage Makes a Difference!

Voltage is on atomic and biological length and time scale
so clamping the voltage changes
NATURAL FUNCTION in mitochondria

Just as it does in Nerve Fibers.

Fluxes in Channels interact by CHANGING
(i.e., Unnclamping) the voltage.

Fluxes in mitochondria interact by CHANGING
(i.e., Unnclamping) the voltage.

Clamping Voltage Changes Things!

Fluxes in Nerve Channels interact by CHANGING
(i.e., Unnclamping) the voltage.

Fluxes in mitochondria interact CHANGING
(i.e., Unnclamping) the voltage.

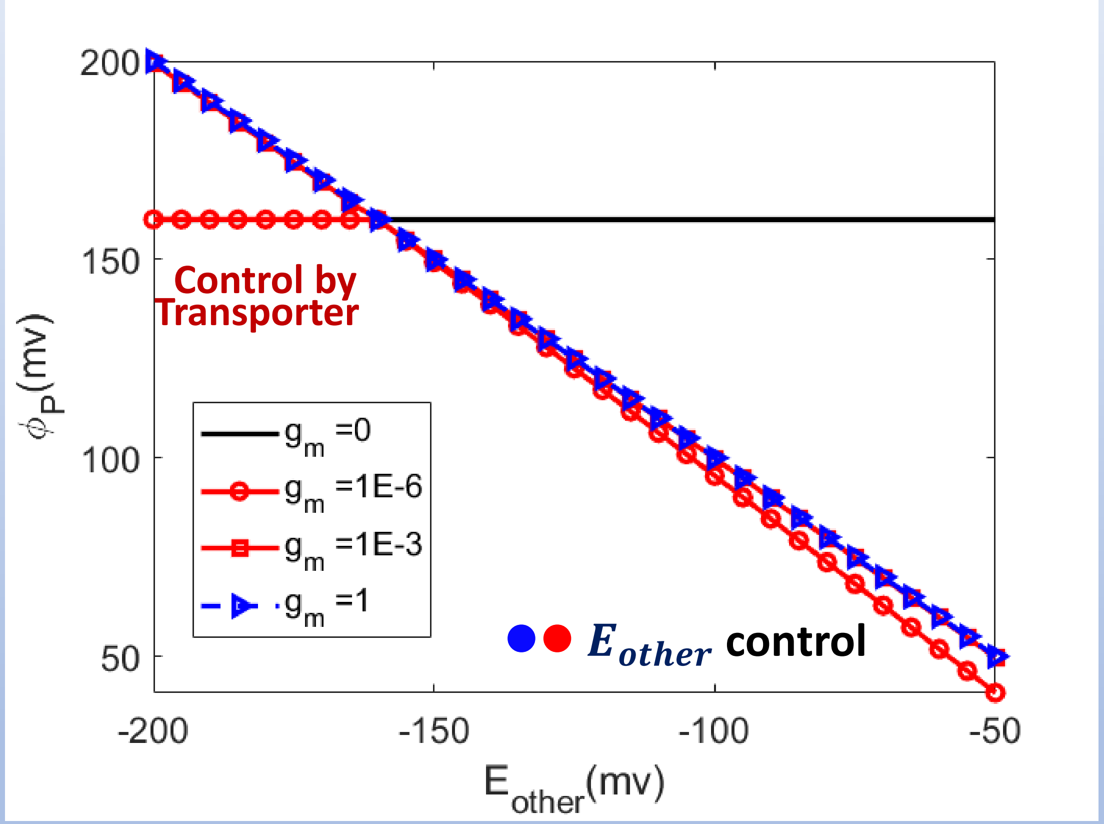
Flux ratios depend on MACROSCOPIC as well as ATOMIC Interactions

Flux Ratios do NOT estimate atomic scale reaction constants

Classically DEFINED rates are different in Voltage Clamped and Unclamped Conditions

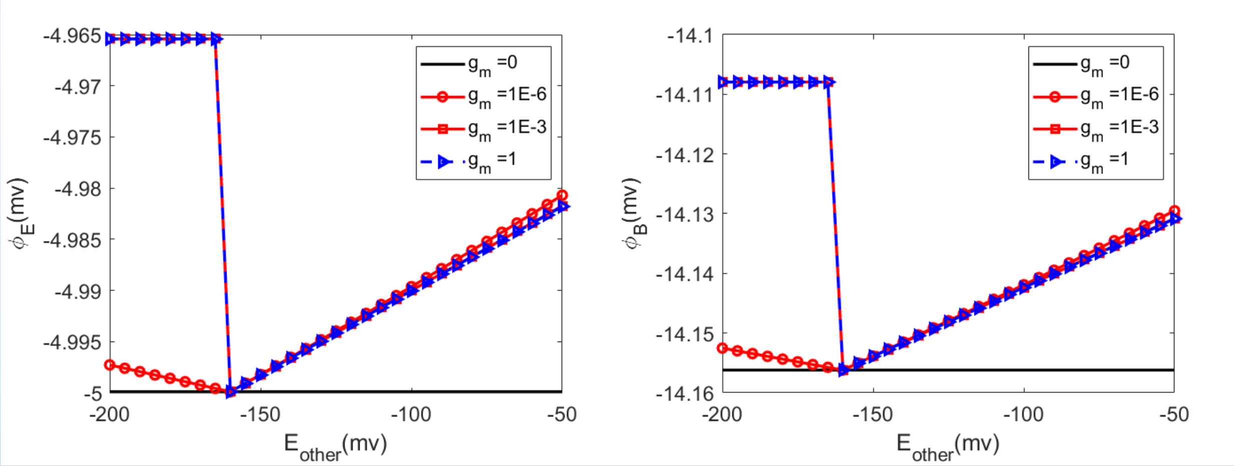
BLUE is Clamped by E_{other}= V_{clamp}

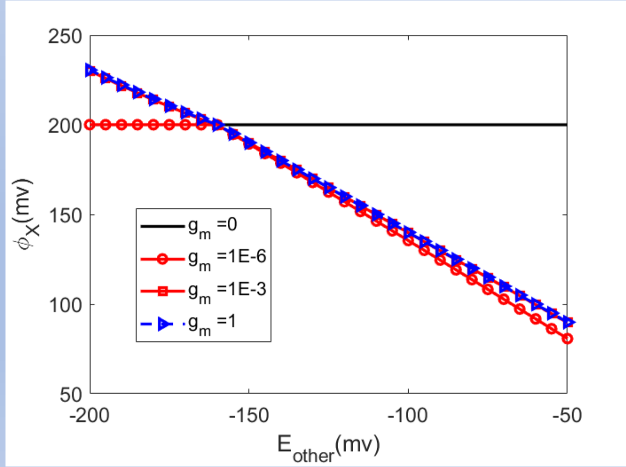
Red is UNclamped

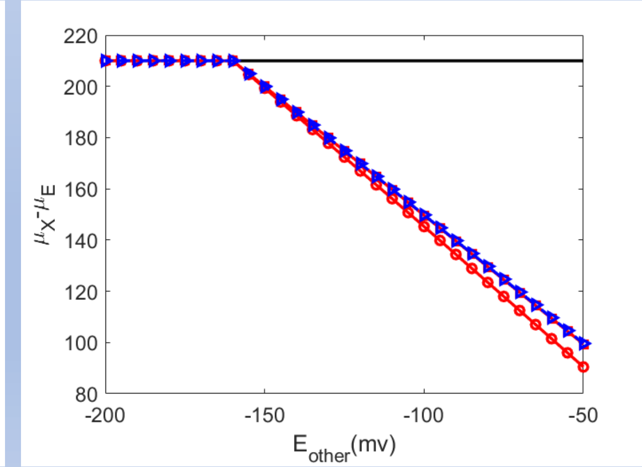


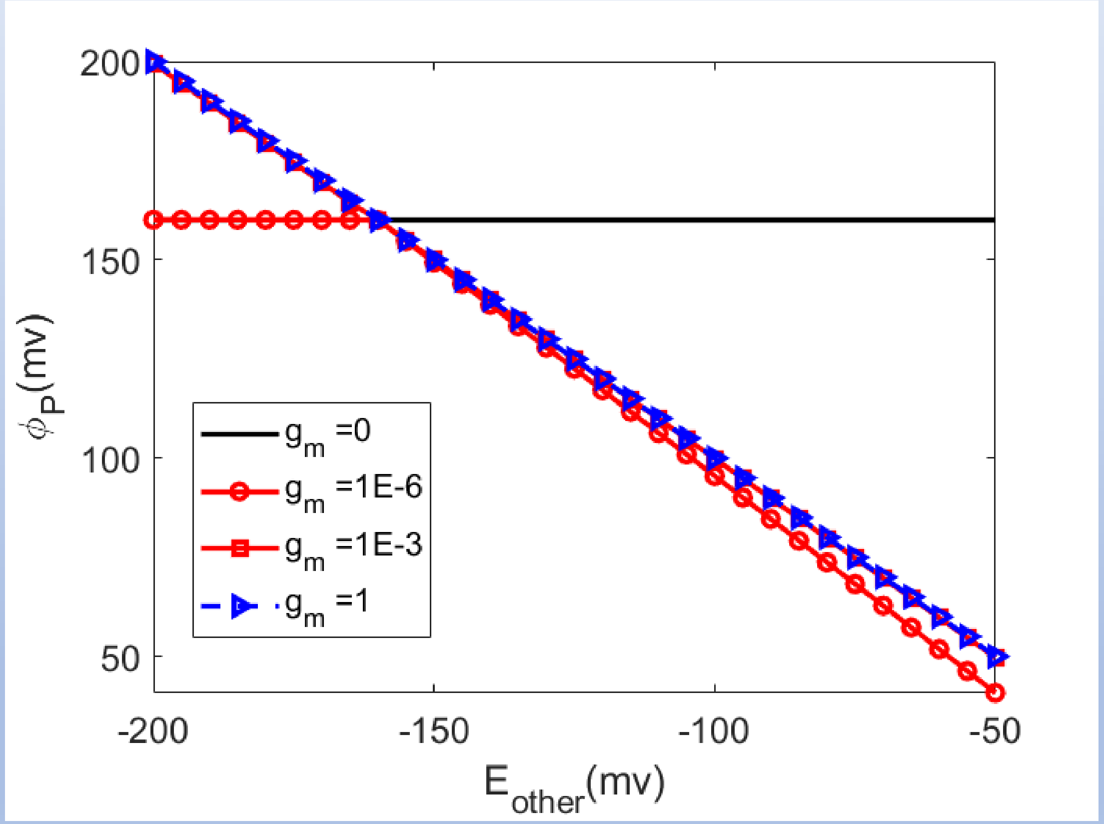
$$\delta_{th} = 210mv$$

Effects of E_{other}= V_{clamp} under different (g_m, δ_{th})







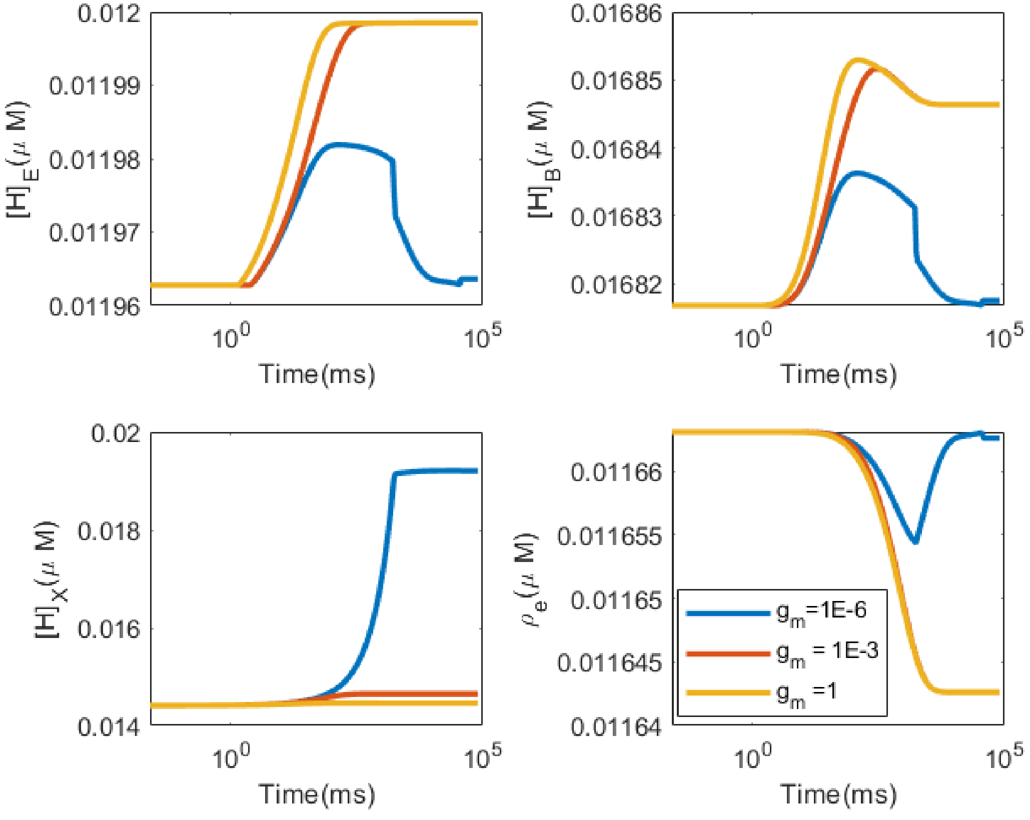


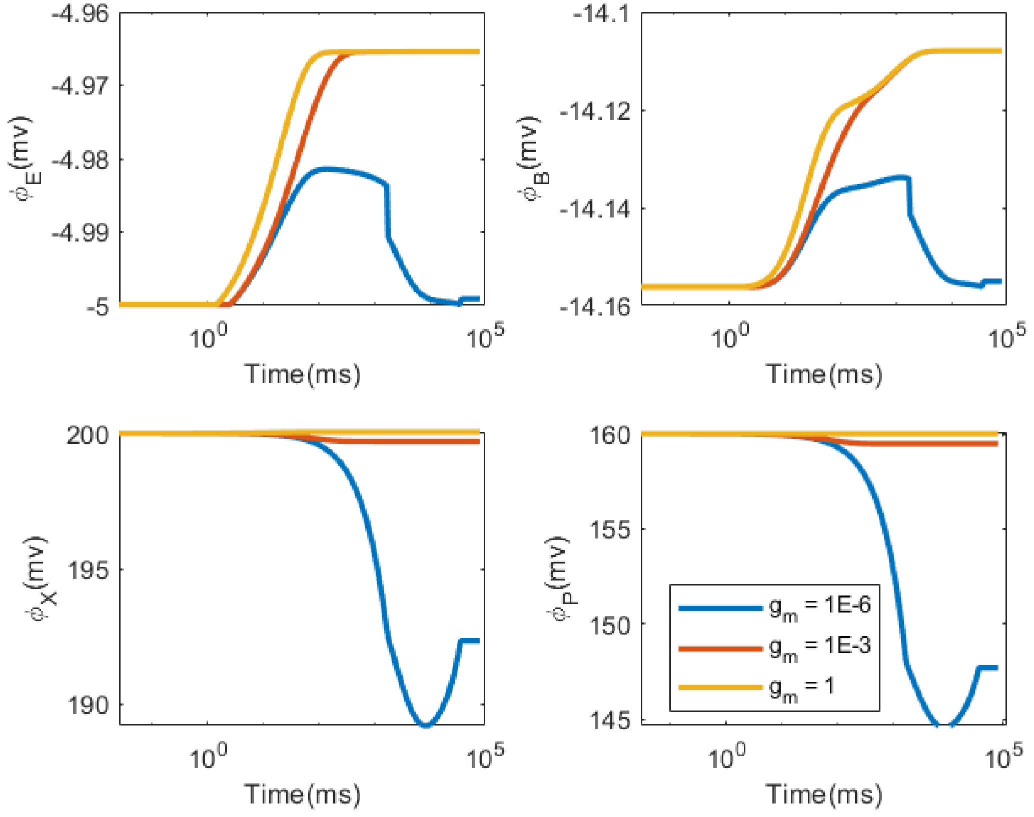
$\delta_{th} = 210mv$

High $[H^+]_P$

BLUE is Unclamped

Brown is clamped by E_{other}= V_{clamp}

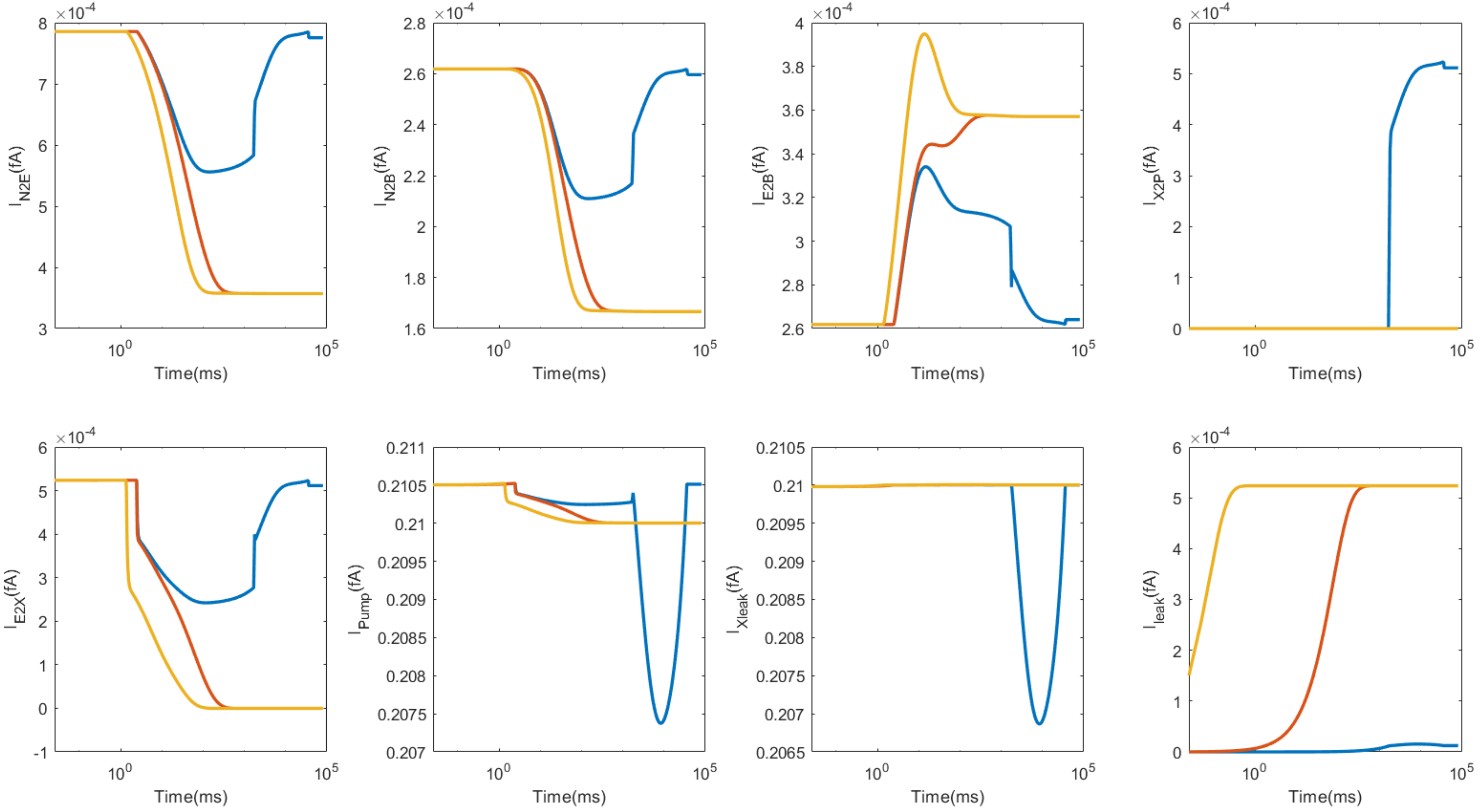




High $[H^+]_P$

BLUE is Unclamped

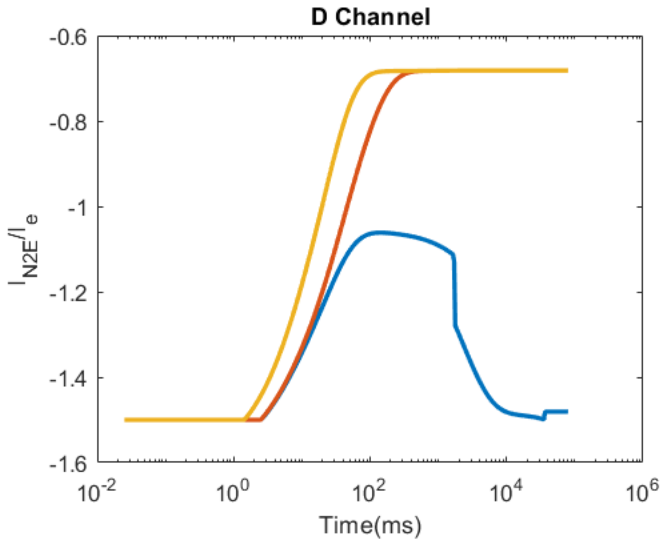
Brown is clamped by E_{other}= V_{clamp}

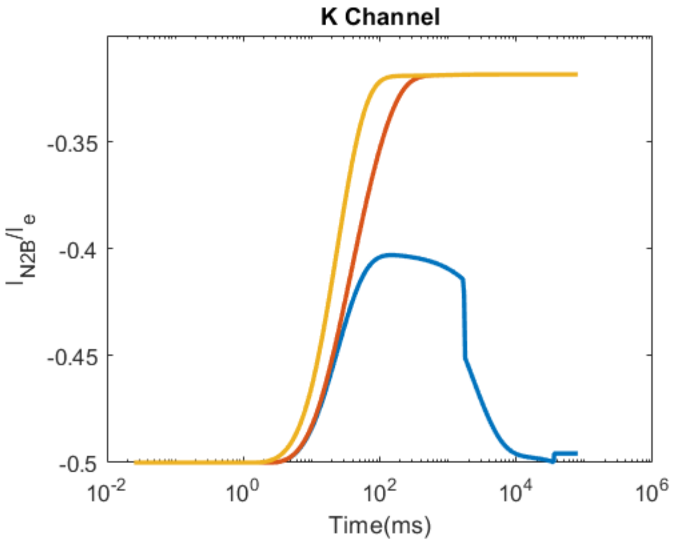


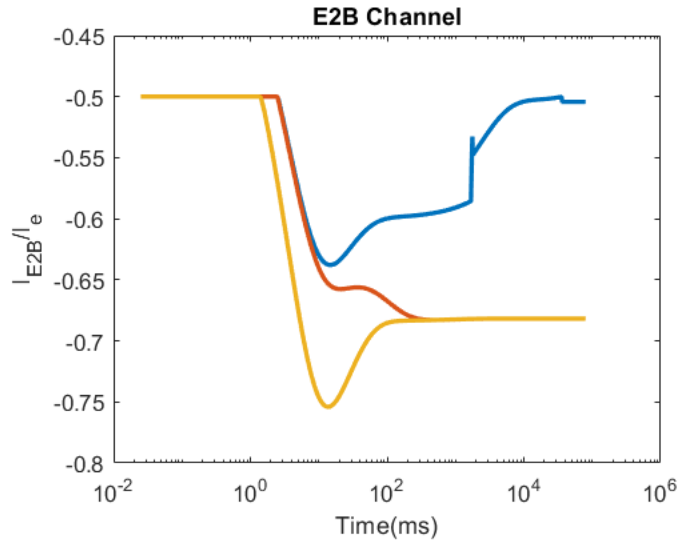
High $[H^+]_P$

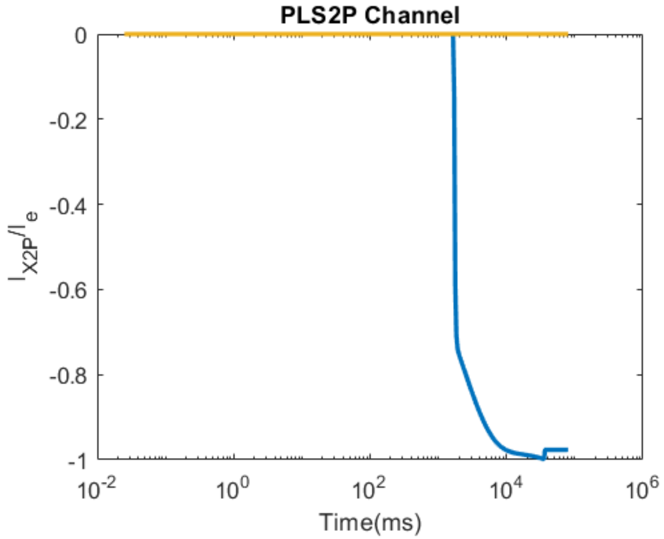
BLUE is Unclamped

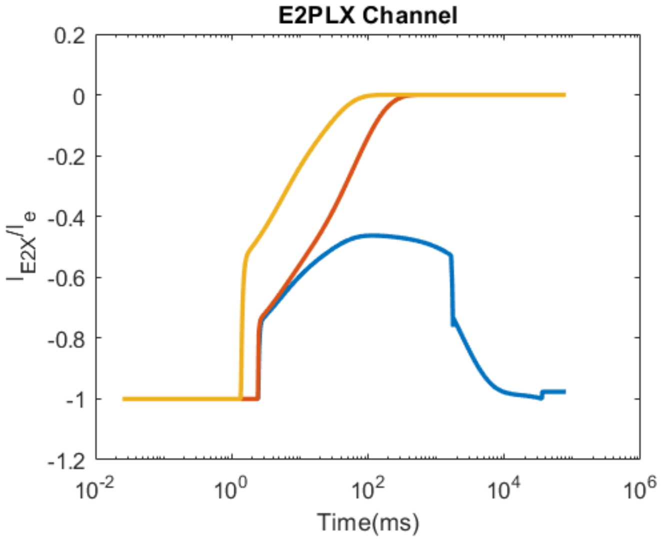
Brown is clamped by E_{other}= V_{clamp}

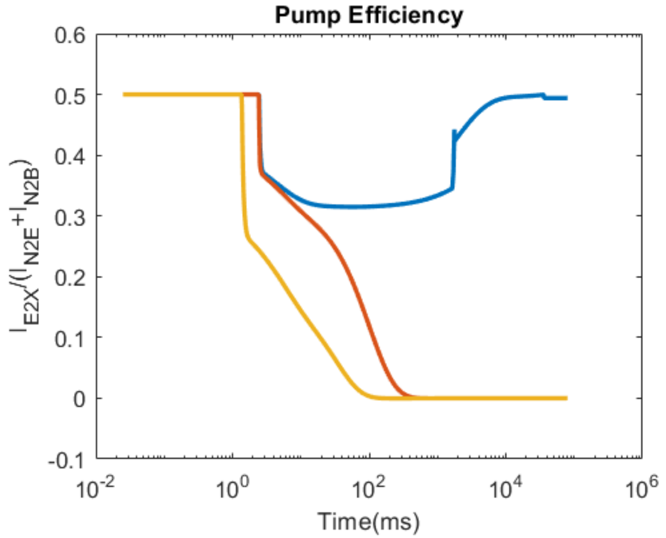








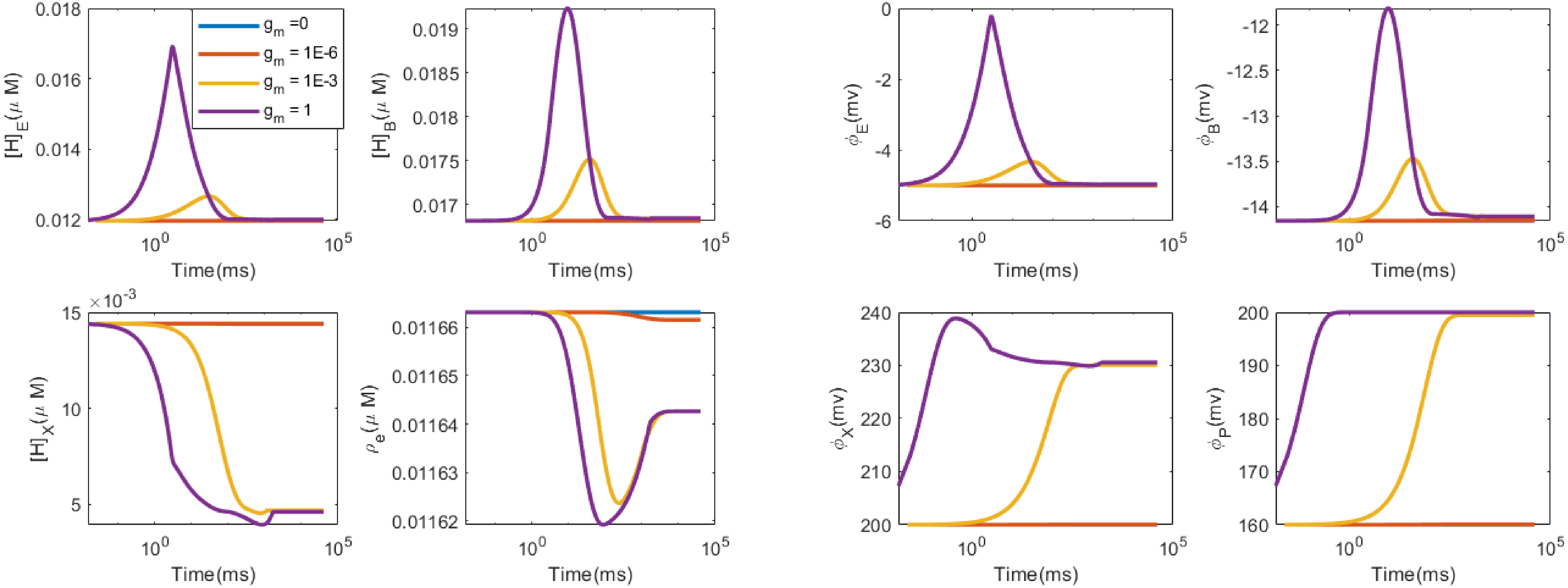




High E_{other}

BLUE is Unclamped

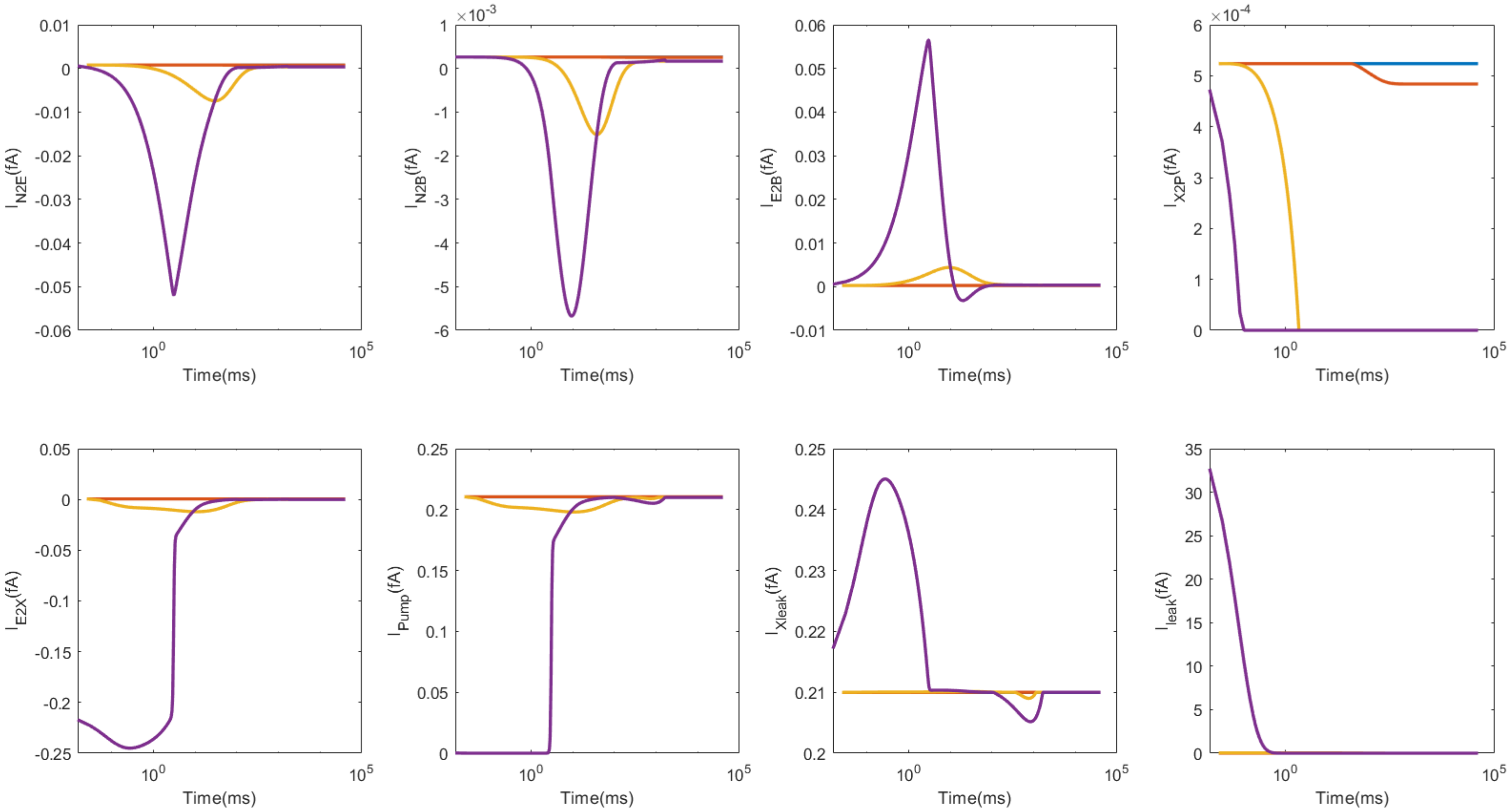
Brown is clamped by E_{other}= V_{clamp}



High E_{other}

BLUE is Unclamped

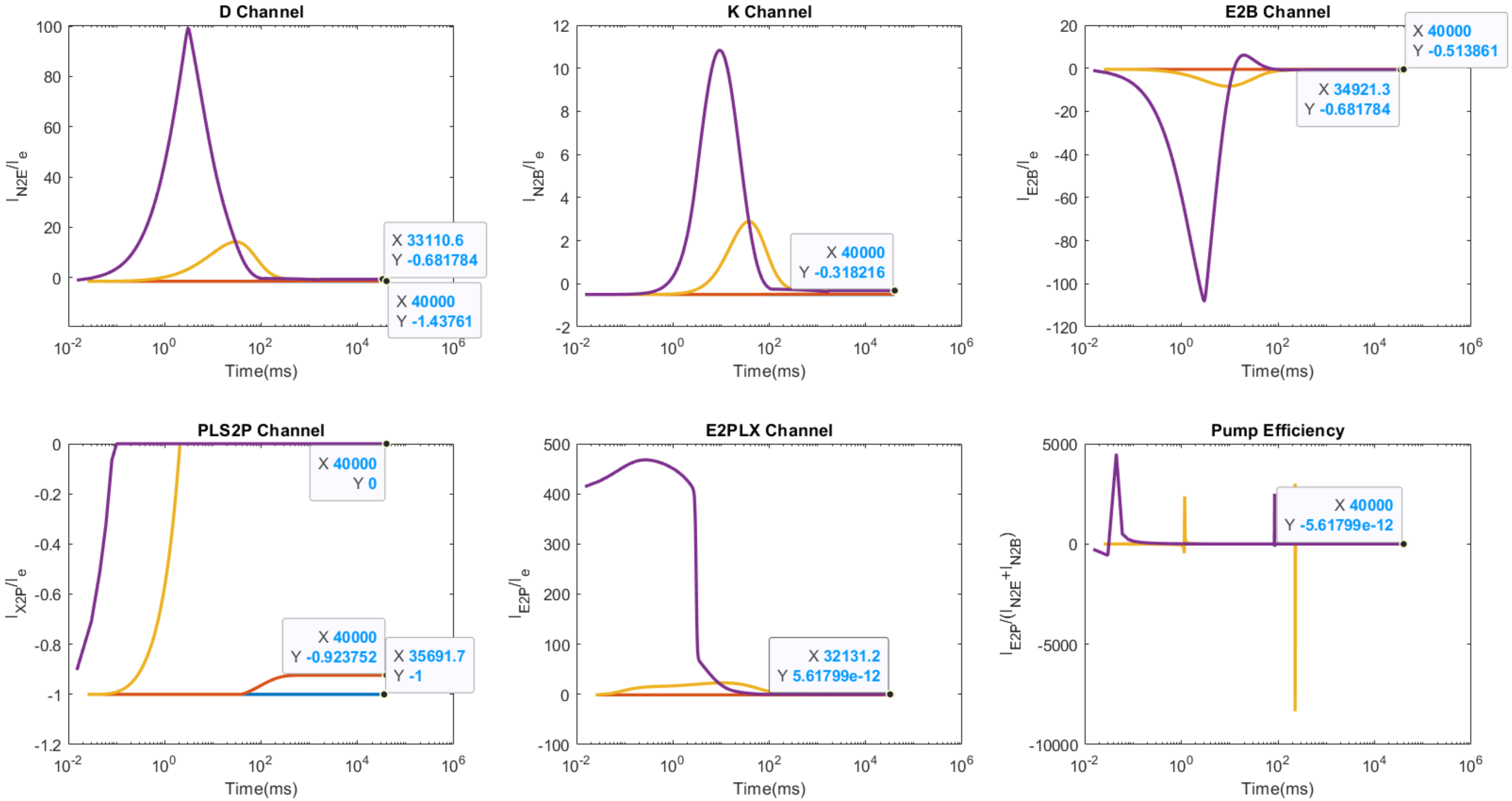
Brown is clamped by E_{other}= V_{clamp}



High E_{other}

BLUE is Unclamped

Brown is clamped by E_{other}= V_{clamp}



Any Questions?